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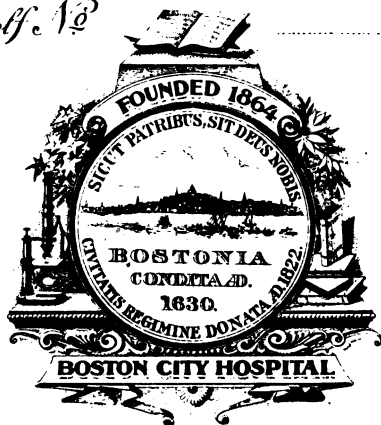
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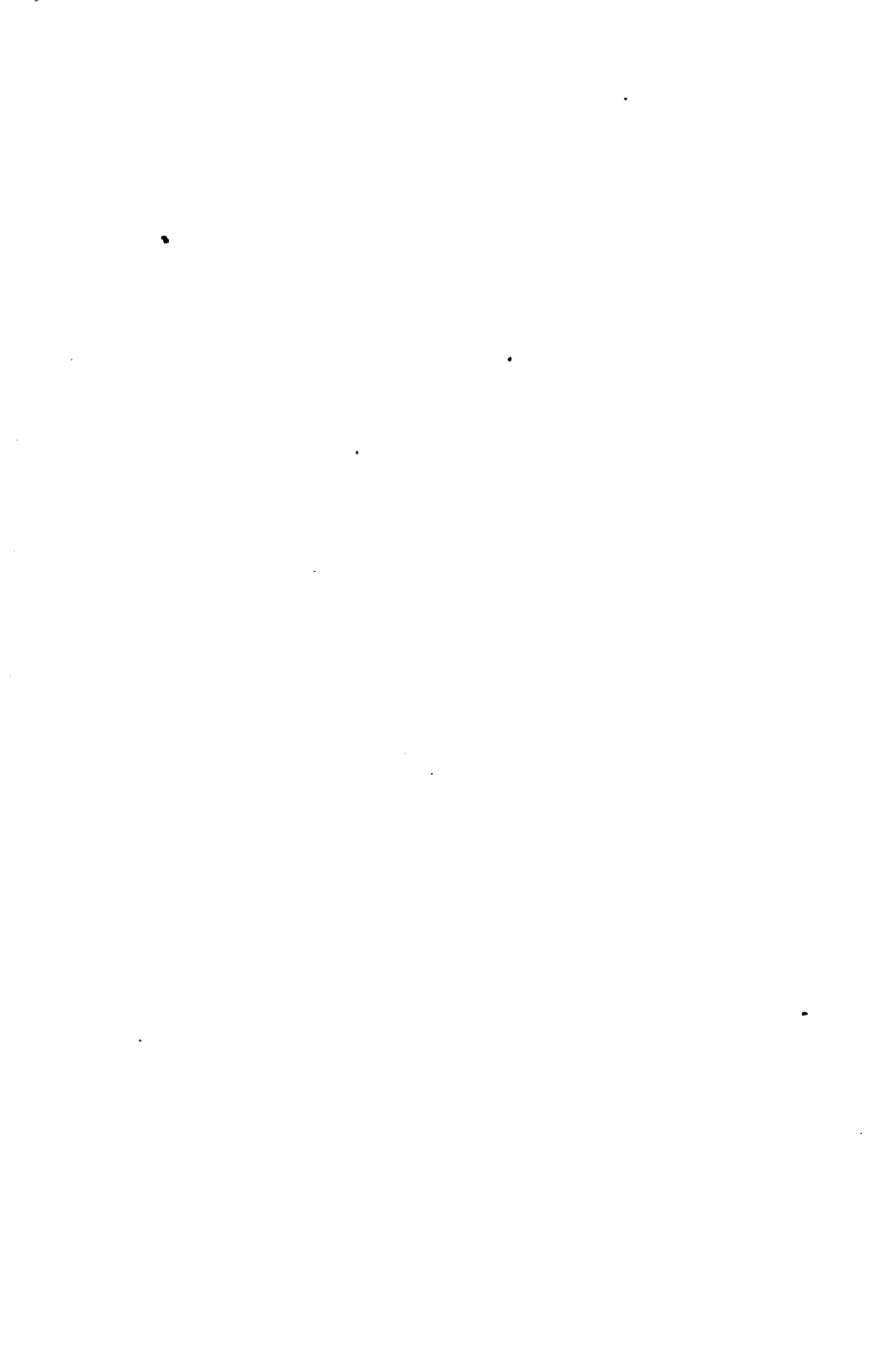
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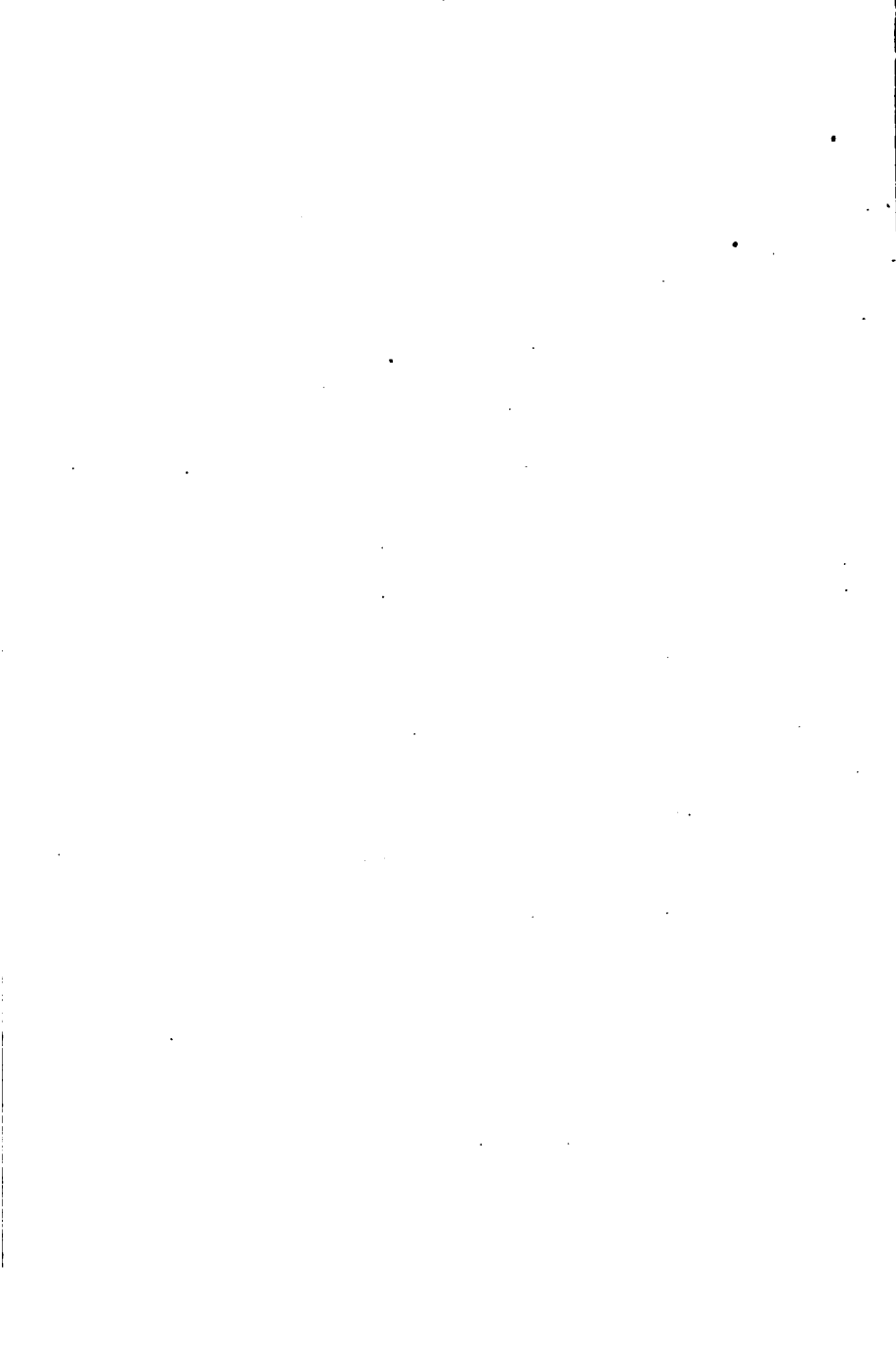
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ATLAS AND EPITOME
OF
SPECIAL PATHOLOGIC HISTOLOGY

BY
DOCENT DR. HERMANN DÜRCK
ASSISTANT IN THE PATHOLOGIC INSTITUTE; PROSECTOR TO THE MUNICIPAL
HOSPITAL L. I. IN MUNICH

AUTHORIZED TRANSLATION FROM THE GERMAN

EDITED BY
LUDVIG HEKTOEN, M.D.
PROFESSOR OF PATHOLOGY IN RUSH MEDICAL COLLEGE, CHICAGO

LIVER; URINARY ORGANS; SEXUAL ORGANS
NERVOUS SYSTEM; SKIN; MUSCLES; BONES

With 123 Colored Illustrations on 60 Lithographic Plates

PHILADELPHIA AND LONDON
W. B. SAUNDERS & COMPANY

1901

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EDITOR'S PREFACE.

As stated in the author's preface, this volume completes Special Pathologic Histology. The third and remaining volume will deal with General Pathologic Histology. I believe that the present volume fully maintains the standard set by the first, and that medical students as well as physicians will find the volumes a great help in arriving at a satisfactory understanding of the anatomic changes caused by disease. The notes I have inserted are inclosed in brackets.

LUDVIG HEKTOEN.



AUTHOR'S PREFACE.

THIS, the second volume of *Special Pathologic Histology*, the issue of which has been unavoidably delayed, includes the liver, the urinary organs, the sexual organs, the nervous system, the skin, the muscles, and the bones.

The two volumes now constitute a definite whole, for the present complete in itself.

The third volume, which will appear toward the end of 1901, is to contain an exposition of *General Pathologic Histology*.

Naturally, the same viewpoints which guided in the preparation of the text and the selection of the illustrations for Volume I have served also for this volume.

Especial stress has been laid upon the logical connection between the changes recognizable microscopically and the resulting macroscopic appearances because it was thought that this would best meet the needs of the beginner and best further an understanding of the genesis of pathologic changes in the organs.

The pathologic histology of the organs of special senses has not been discussed, for the reason that it is made the subject of separate text-books. The more important and more frequent diseases of the skin have been taken into consideration, as the changes in the skin often appear quite

striking after death, and are frequently made the subject of anatomic investigation.

The system diseases of the central nervous system have been left out wholly because they are treated fully elsewhere, and on the other hand because the general histologic changes in variously localized processes with different courses correspond in the essentials.

The complete field of genuine neoplasms is reserved for the General Pathologic Histology. Certain tumors occurring only in connection with definite organs are described in conjunction with these organs ("hypernephroma," "adenomyoma of the uterus").

For the index to Volumes I and II, I am indebted to my colleagues, Dr. Oberndorfer and Dr. Marz. Dr. Hutzler and Dr. Dörr have assisted with the proofs, and for this service I thank them warmly.

HERMANN DÜRCK.

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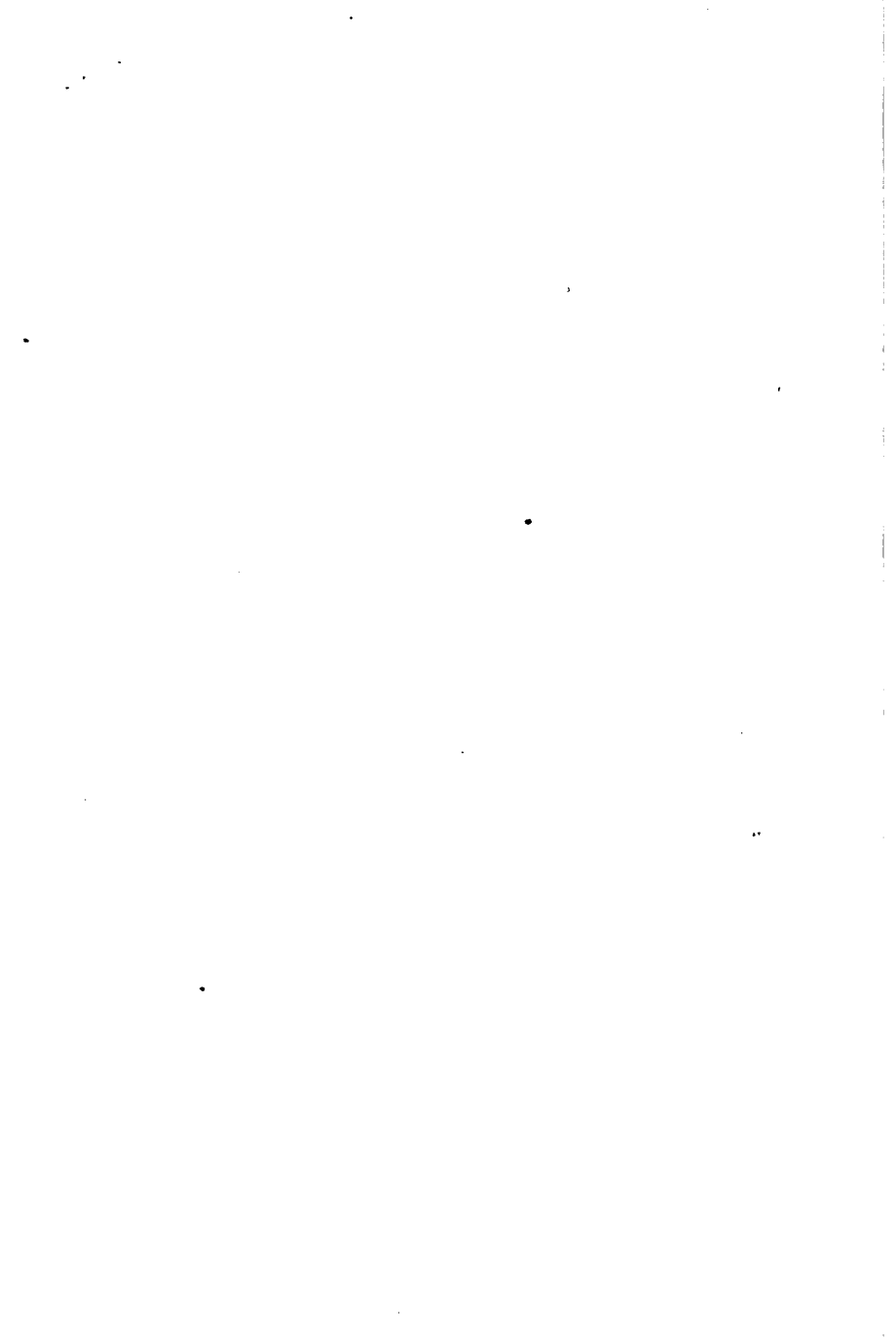
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PATHOLOGIC HISTOLOGY.

THE LIVER.

The liver is a gland whose original tubular structure has been modified in a peculiar way in the highest vertebrates and in man, in that the finest ducts, the biliary capillaries, are not formed by a complete and distinct cellular cylinder, as in other tubular glands, but are embedded each between two rows of liver cells.

A magnifying lens of low power, or even the naked eye, very generally, but not always, detects upon the cut surface of the normal human liver a finely variegated marking—darker round points appear to be surrounded by lighter zones. This marking corresponds to the hepatic lobule. Each liver lobule is about 0.7 to 2.2 millimeters in diameter, and shows on transverse section a distinctly radiate structure. The center is formed by a thin-walled vessel, the vena centralis, into which empty from all sides the capillaries of the portal vein. The spaces between the capillaries are occupied by columns of liver cells, in man arranged mostly in a double row. The columns occasionally anastomose, thus forming longish spaces for the capillaries. In man the individual lobules are not distinct from one another, but pass one into the other without precise borders, the cell columns of one lobule passing directly into adjacent lobules. Only at certain points upon the peripheries of the lobules, which in man mostly are triangular in outline, appear connective-tissue trabeculae, which support blood-vessels—branches of the portal vein and of the hepatic artery—and the interlobular bile ducts. The

number of lobules in the human liver is somewhat more than three-quarters of a million.

Each liver cell is 15 to 30 microns in diameter and cubical or polygonal in form, without membrane, the finely granular protoplasm becoming more dense toward the surface, the nucleus being vesicular and globular with a faint network of chromatin. Often one cell contains two nuclei, probably the result of direct division. The protoplasm, especially of the cells in the outer parts of the lobules, very frequently normally contains fine droplets of fat. Other cells, more particularly those in the central parts, contain small, yellowish-brown pigment patches.

The relations of the liver cells to the blood capillaries and to the bile capillaries are peculiar. The biliary passages pass into the interior of the lobules as fine canals without walls and run along the lateral surfaces of the cords of liver cells, each surface of which presents a trough-like depression, which, with a similar depression in the neighboring cell, forms the biliary capillary. Each liver cell consequently is in contact with as many biliary capillaries as it has lateral surfaces. The blood capillaries, on the other hand, run along the margins of the liver cells, and are thus removed from the biliary capillaries by half a cell's breadth.

In addition, there is within the lobules a small quantity of reticulum in the form of very fine fibrillæ of collagenous nature, which lie between the rows of liver cells and the blood capillaries, being parallel with the latter, and united, on the one hand, with the wall of the central vein, and, on the other, with interlobular bands of fibrous tissue.

Along the walls of the blood capillaries lie rather large, star-shaped or pyramidal cells, the so-called stellate cells, or Kupffer's cells, which are faintly visible only under certain conditions, and probably must be regarded as modified vascular epithelial¹ cells.

¹ Throughout this book epithelial is used as synonymous with endothelial in speaking of the cells lining vessels.

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For practical reasons three zones, not anatomically distinct, are distinguished in the liver lobule: (1) The central zone, about the vena centralis; (2) the peripheral or portal zone; and (3) the intermediate zone, between the first two. As certain depositions, often visible macroscopically, may limit themselves to certain zones, these, as well as the lobular markings in general, may become especially distinct under pathologic conditions.

As stated in the preface to vol. I, a certain amount of training may enable one to draw from the macroscopic picture definite conclusions as to the finer changes in the elementary constituents, and this is particularly true of the liver. The state of the lobular markings furnishes a very important criterion for the demonstration of some of the pathologic conditions of the organ. The mutual demarcation of the liver lobules, their color, size, and form, in many cases may be recognized with the naked eye, and are of the greatest importance in diagnosis.

CIRCULATORY DISTURBANCES OF THE LIVER.

In the cadaver an unequal distribution of the blood in the liver is often the case. In persons that have died suddenly, as by accident or suicide, the cut surface is usually a homogeneous grayish-brown or grayish-blue, according to the period of digestion and the general amount of blood. In such normal livers the lobular markings are hard to recognize, and, accordingly, the microscopic sections show a quite uniform amount of blood in the intralobular capillaries. The findings are quite different in those cases in which death occurs after prolonged agony and a gradual failure of the heart. As the cardiac power sinks, the inferior vena cava is unable to empty itself completely into the right auricle, and the resulting congestion naturally extends into the hepatic veins, which become dilated to their finest radicles, the venæ intralobulares, and even the capillaries in the central parts of the lobules may be congested. The increased amount of blood

and the dark red color of the centers of the lobules render them quite distinct from the peripheral portions. This condition is observed in most cadavers, and must not be regarded as a genuine passive congestion of the liver, in which there is always atrophy of the liver cells around the central veins. Microscopic examination of suitable sections will show that this atrophy is absent in "agonal congestion."

Genuine passive congestion of the liver occurs after a lasting obstruction to the flow of the blood in the vena cava inferior, whether caused from pressure upon this vessel by tumors, by pleural and pericardial exudates, etc., by valvular disease of the heart, or by insufficiency of the left ventricle, as may develop in emphysema. The dilatation of the hepatic veins is now permanent and usually progressive, and it shows itself in each and every lobule by dilatation and congestion of the central vein and of the adjacent portions of the portal capillaries. In fresh sections in which the blood has not been washed away, or in fixed specimens in which the blood has been preserved, the cross-sections of the lobules present roundish or irregular-shaped areas, mostly occupied by red corpuscles, the columns of liver cells being compressed and more or less completely absent according as the circulatory disturbance has been of longer or shorter duration. In advanced cases the liver tissue in the central part of the lobules may become wholly atrophied, so that the walls of the greatly dilated capillaries come into contact and form cavernous vascular spaces, which appear to be continuous. The longer the congestion lasts, the further toward the periphery of the lobules does the capillary dilatation extend, and in many places the prolongations of the deep red areas of congestion in adjacent lobules touch one another. In this way the parenchyma of the organ is compressed into smaller and smaller volume, and at last there are but scattered islands of liver tissue between the confluent vascular spaces which form unbroken networks.

PLATE 61.

FIG. 1.—**Passive Congestion of Liver.** $\times 54$. The figure shows almost four acini, cut transversely, the peripheral zones coalescing without sharp borders: 1, Venæ centrales; 2, central zones of portal capillaries dilated with blood corpuscles so that the cords of liver cells in these areas are no longer distinct.

FIG. 2.—**Congested and Fatty Liver in Stage of Atrophy.** $\times 170$. Sector of acinus cut transversely: 1, Vena centralis; 2, central zone—cords of cells interrupted, the portal capillaries expanded into cavernous spaces filled with blood corpuscles; 3, cords of cells in peripheral zone filled with vacuoles corresponding to the extracted fat drops.

This condition is known as “red atrophy,” cyanotic atrophy, or as passive congestion of the liver with atrophy. Occasionally it may be associated with an increased infiltration of fat in the outskirts of the lobules at the same time as there is a deposition of brownish blood pigment in the congested centers and the connecting prolongations, due to continuous but slow hemorrhages by diapedesis. This renders the macroscopic color distinctions of the various zones of the lobules very sharp and distinct upon the fresh cut surface: deep red flecks and bands alternate with yellowish-gray and grayish-brown islands, and between the two is a sharp contrast. Now one speaks of passive congestion with fatty infiltration, the condition being appropriately designated as “nutmeg liver,” because of the similarity of the cut surface to that of the fruit of the nutmeg tree. Frequently the surface is also very finely granulated (*cirrhose cardiaque*, *foie cardiaque* of the French authors).

As elsewhere in the body, long-continued congestions of the liver lead to a real hyperplasia of fibrous tissue. The dilated capillaries in the centers of the acini come into contact as the intervening columns of liver cells disappear, and proliferation in the walls of the hepatic veins leads to formation of a fibrillated connective tissue, often infiltrated

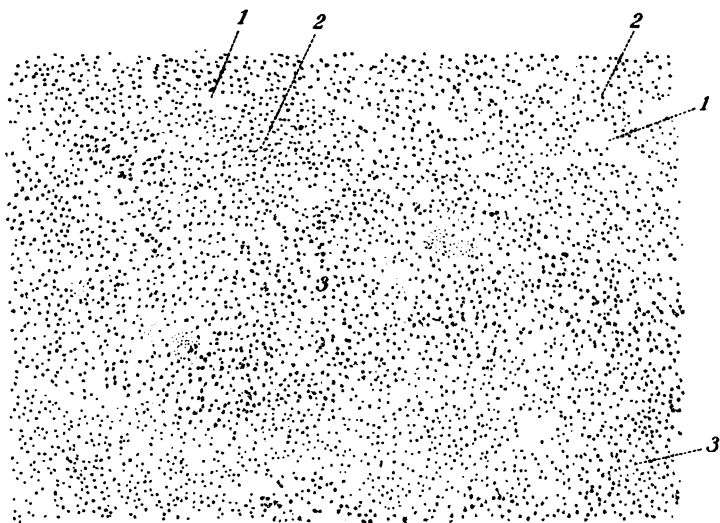


Fig. 1.

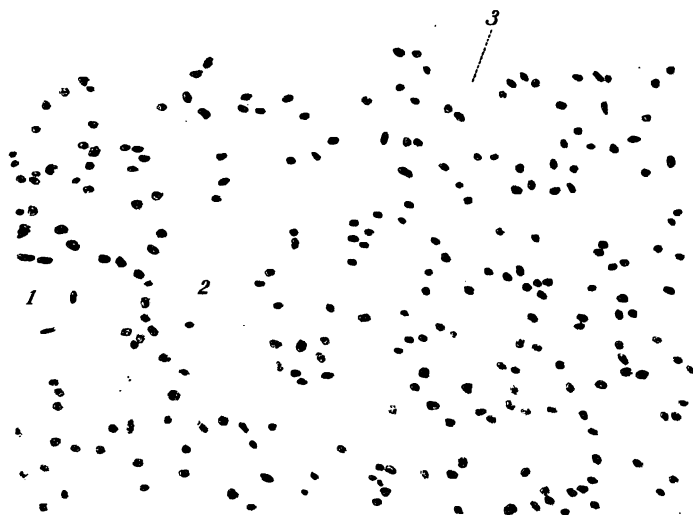
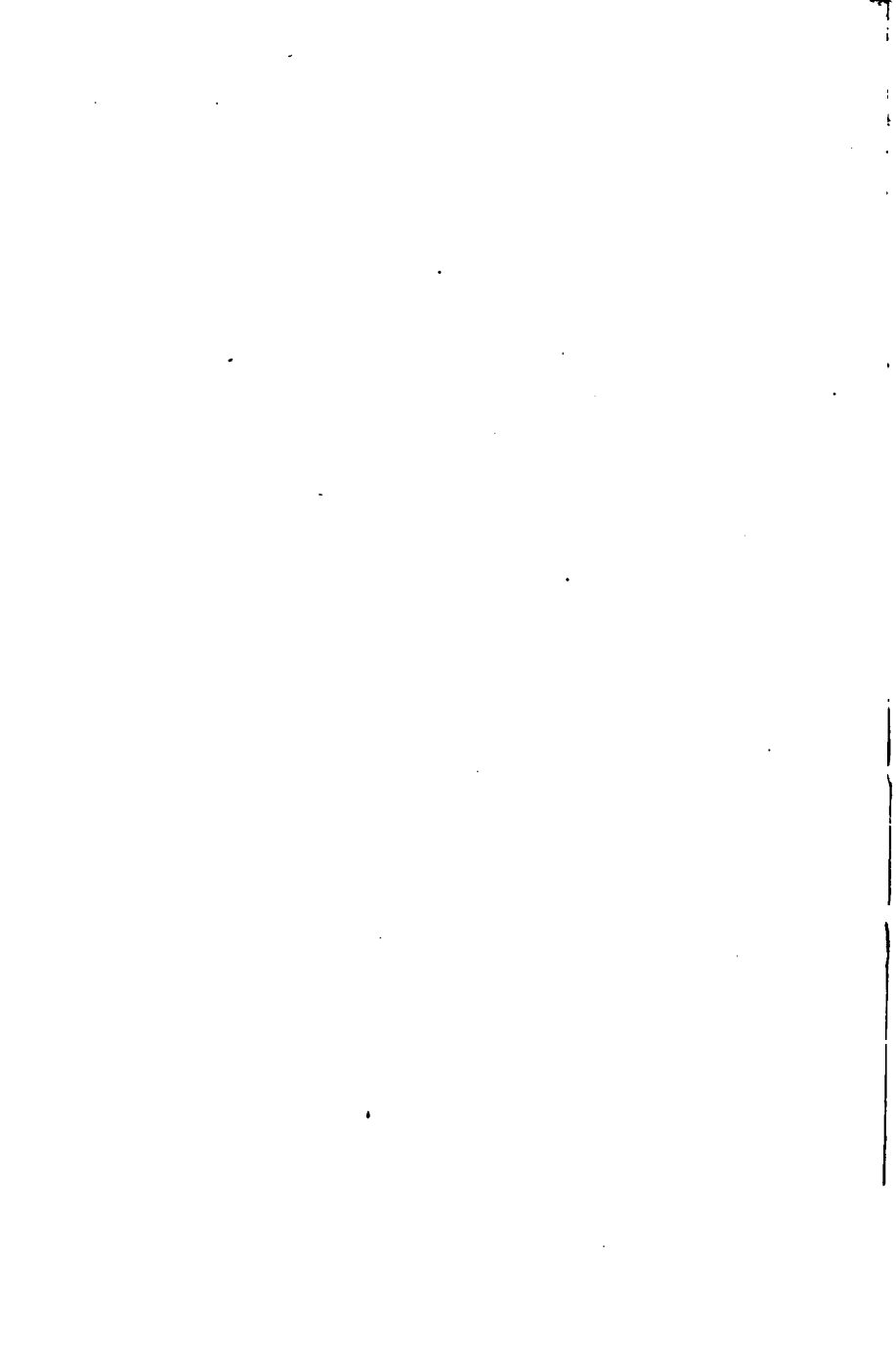


Fig. 2.



with round cells, which grows outward in a radiating manner between the cavernous capillary spaces, whose walls also increase in thickness. And the interacinous connective tissue around the branches of the portal vein may also proliferate, so that a diffuse increase in the consistency of the liver takes place (passive congestion with induration), and in the microscopic sections it is now often difficult to separate the lobules one from another.

Later appear in the connective tissue newly formed biliary channels, formed partly by epithelial proliferation, partly by atrophy of the columns of liver cells—a process encountered in many pathologic conditions in the liver associated with parenchymatous atrophy.

INFARCTS IN THE LIVER.

The peculiar vascular arrangement in the liver, especially the presence of two centripetal systems (*vena portæ* and *arteria hepatica*), does not permit of a ready formation of infarcts in this organ. Even complete thrombotic or embolic occlusion of the portal vein does not lead to infarction under normal conditions; for the so-called “internal portal radicles,” which communicate with the hepatic artery, obviate the resulting interference with the supply of blood, and the occlusion of larger branches of the portal vein does not usually lead to severe nutritive disturbances.

In the presence, however, of certain general circulatory disturbances, especially general venous congestion from diminished propulsive power of the left ventricle, thrombotic or embolic occlusion of the portal branches results in a change, which, following Zahn, has been designated as “atrophic red infarct.” These are not infarcts in the usual sense, but foci of hyperemia, which, except for their being definitely circumscribed, in nowise differ from the pictures presented in the red atrophy of passive congestion. They may arise rapidly, and are occasionally,

though rarely, associated with small hemorrhages. Necrosis of liver tissue never occurs, but only atrophy of cellular columns in the central as well as often in the intermediate zones of the lobules.

On the other hand, occlusion of the smallest interlobular branches of the portal vein lead to minute, multiple foci of necrosis in the liver, with or without hemorrhage, because the branches of the hepatic artery cannot now furnish compensatory supply through the "internal radicles." Puerperal eclampsia is especially productive of multiple foci of necrosis in the liver, due, presumably, to multiple hyaline thrombosis of the interlobular branches of the portal vein on account of the general intoxication, which gives rise to coagulative substances (Schmorl) (Plate 68, Fig. 2). Various other diseases of septic nature, especially gangrenous processes in the territory drained by the radicles of the portal vein, and certain intoxications (arsenic) may lead to multiple necroses in the liver.

In these cases histologic examination of the liver, which to the naked eye appears sprinkled with fine yellow flecks, reveals circumscribed areas of necrosis with more or less advanced disintegration of the cells. The nuclei of the liver cells in these areas do not take the stain, while the nuclei of the capillary epithelium and of the leukocytes in the blood-vessels for some time still react normally with stains. In the earlier stages the lobular structure is fairly well preserved, but eventually the foci disintegrate into a structureless or finely granular mass.

Finally, genuine infarcts in the liver may develop from obstruction of smaller branches of the hepatic artery. In very rare instances occlusion of the entire hepatic artery leads to necrosis of the whole liver (Chiari, Cohnheim, and Litten). Small, sharply circumscribed, insular necroses are more frequent. These differ from the necroses caused by obstruction of the interlobular branches of the portal vein in that the connective tissue which surrounds the interlobular branches of the portal vein, the

hepatic artery, and the bile ducts also undergoes necrosis, so that the necrotic area does not follow the outlines of the lobules. Occasionally the necrotic district becomes surrounded or infiltrated with red corpuscles, giving the picture of a hemorrhagic infarct (see the volume on "General Pathologic Histology").

The changes enumerated in the foregoing take place when the necrosis results from the mechanical effects of embolic (or thrombotic) occlusion of a definite vascular channel. When embolism is caused by infectious material,—*e. g.*, septic or gangrenous thrombi from the portal radicles (or from the umbilical vein in the newborn),—or by plugging of the hepatic artery in acute endocarditis, then a suppurative process may be instituted around the embolus even before necrosis develops. In this manner originates the embolic abscess of the liver. The abscesses that develop in the territory of the hepatic artery, especially in acute endocarditis, are mostly single and minute, while the purulent foci of suppurative pylethrombophlebitis usually are numerous and larger. Such abscesses in the periportal (Glissonian) tissue may be outlined as follows: The center of the foci is occupied by closely aggregated pus cells interspersed with balls or cloud-like heaps of micro-organisms, mostly streptococci or staphylococci, and surrounded by a zone of varying width of necrotic tissue without definite structure, external to which there is infiltration of the tissue with leukocytes with occasional heaps of cocci. The surrounding liver tissue shows the effects of pressure, the columns no longer having a radial arrangement, but being pressed together and rearranged in concentric layers parallel to the surface of the abscess (Plate 69, Fig. 2). [Under the direct influence of various toxins in the blood, of bacterial, vegetable, or animal nature, small foci of necrosis may develop in the liver as well as in other organs—the so-called focal or insular necrosis.]

Suppurative inflammations of the liver may develop

also by way of bile ducts, especially in typhoidal and dysenteric processes in the intestines, or in consequence of inflammatory changes in the bile ducts from the presence in them of biliary concretions, and occasionally from the entrance into the larger ducts of intestinal parasites. In this case, also, the suppuration begins in the periportal connective tissue, considerable quantities of bile being usually mixed with the pus, which on that account has a greenish-yellow appearance and contains brownish and greenish pigment particles. Liver abscesses of this mode of origin contain mostly colon bacilli, which may be seen passing in thick swarms into the surrounding tissue (suppurative cholangitis and pericholangitis). There is a large, so-called primary abscess of the liver, seen especially in the tropics, which also takes its origin from the bile ducts, and in which amebæ are found occasionally.

ACUTE PARENCHYMATOUS HEPATITIS (CLOUDY SWELLING).

Acute parenchymatous hepatitis [so called by the Germans] is applied to a process which expresses itself far more in purely degenerative than inflammatory changes—namely, cloudy swelling of the liver [and this is by far the better term]. It is found in infectious diseases, especially in septicemia, puerperal fever, typhoid fever, recurrent fever, erysipelas; and also in pneumonia, scarlatina, diphtheria, and malaria; furthermore, in certain intoxications, such as with phosphorus, chloroform, chloral; and also in poisoning by mushrooms and other fungi, more particularly *Amanita phalloides*.

Macroscopically the liver is enlarged, soft, and friable. The sharp corners and margins of the cut surfaces are rounded; the swollen parenchyma is opaque, grayish-brown, and looks as if it had been boiled. The amount of blood present is small, and the lobular markings are obliterated.

Only fresh specimens—teased preparations, frozen sec-

tions, or sections cut with the double-bladed knife—are suitable for microscopic examination, as the characteristics are lost wholly in fixed material. The liver cells are enlarged, the cubical outline more rounded, and in advanced stages many are swelled like balloons. The normal granulation of the protoplasm is greatly increased, the entire protoplasmic contents being usually uniformly clouded by the presence of innumerable, fine, dust-like points, the nucleus wholly covered, invisible or but indistinctly recognizable. In advanced instances the vascular epithelium also is involved in this process, and at times teased preparations show Kupffer's cells the seat of cloudy swelling (Plate 64, Fig. 1). Occasionally there is seen, in addition to the fine granules, also larger, refractive droplets. The nature of the fine granules is easily determined by the addition of dilute acetic acid or potassic hydrate, which immediately dissolves them, the nucleus becoming distinct, while the larger glistening droplets (fat) remain unchanged. Hence the granular swelling is the result of the deposition of innumerable albuminous particles, which are changed into acid or alkaline albuminates and dissolved in the excess of the alkali or acid. At the same time the arrangement of the liver cells in the acini is disturbed, the cellular columns appear misplaced and thrown into irregular heaps ("dissociation of the cells," Browicz), the regular rows of cells being often interrupted in their course. The whole process may be regarded as a preliminary stage in necrosis or fatty degeneration. Both the latter conditions may be associated with cloudy swelling ("albuminous degeneration"), which in its milder forms is susceptible of a complete recession through absorption. The macroscopic appearances are easily explainable on the basis of the histologic findings: The swelling of the cells causes not only increase in the volume of the whole organ, but also relative anemia of the liver by compressing the intertrabecular capillaries, as well as dissociation of the cords, diminution in consistency, and friability.

PLATE 62.

FIG. 1.—Fatty Infiltration of Liver in Pulmonary Tuberculosis. $\times 54$. The peripheral zones of the acini show the columns of cells full of rounded fat vacuoles and perforated like a sieve: 1, Vena centralis; 2, peripheral zone, infiltrated with fat; 3, interlobular (Glissonian tissue) with branches of portal vein, of hepatic artery, and bile ducts.

FIG. 2.—Fatty Infiltration of Liver in Pulmonary Tuberculosis. $\times 170$. 1, Vena centralis; 2, peripheral zone the liver cells in which contain large vacuoles.

A peculiar termination of cloudy swelling is seen in "acute atrophy of the liver," the anatomic and clinical picture of which is so typical that it is generally regarded as a disease *sui generis*. It is, however, beyond doubt that it may develop after ordinary cloudy swelling of the liver in pyemic and septicemic infections. Its relative frequency in women during pregnancy and puerperium is well established.

The more or less shrunken and flabby liver usually presents, even to the naked eye, two different and distinct substances: extensive yellow, or yellowish-brown ("yellow atrophy") areas, which alternate with deep red; and, on the cut surface, depressed districts, which predominate in the later stages, especially in the left lobe.

Microscopic examination of fresh specimens shows marked disorder of the columns of liver cells and a high degree of fatty change in the protoplasm. Teased specimens from the yellow foci show the cells in part enlarged and rounded, often crowded with great masses of smaller and larger fat droplets and balls (Plate 64, Fig. 2). Nuclei are hardly seen; many cells appear as if they were ruptured, and from them emerge glistening little masses of fat. In addition, they are also always strongly icteric, either from diffuse imbibition of yellowish-green pigment or by deposition of fine, angular granules of biliary coloring-matter. Much free fat is also present, the small

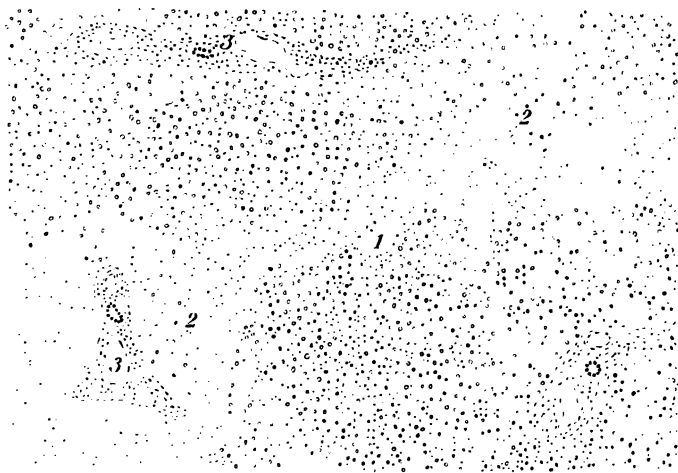


Fig. 1.

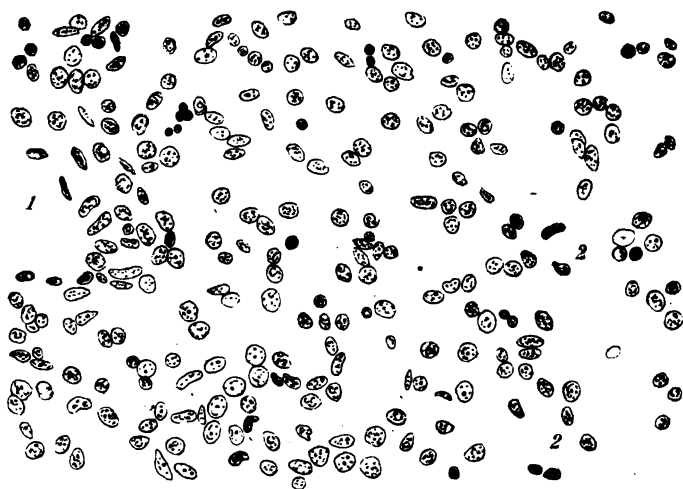


Fig. 2.



droplets often running together into larger globules, as well as free biliary pigment, and often also sheaves of tyrosin crystals, soluble in warm water.

Sections present varying appearances, depending on the age of the process and the places from which they are taken. The complete destruction of the liver tissue obtains in the depressed areas, the nature of the tissue being difficultly recognizable on account of a reticular structure with round openings corresponding to the extracted fat; the nuclei of the liver cells are largely absent, while those of the vascular epithelium are mostly well preserved; scattered about are round cells, either single or collected in heaps (Plate 63, Fig. 1). Hemorrhagic foci are often present. In the less damaged areas the ectatic capillaries frequently contain numerous red corpuscles.

Investigation of the older stages of the process reveals clearly inflammatory and regenerative reactive phenomena. Bordering immediately upon the degenerated tissue, composed mostly of fat vacuoles, are cellular, dense areas, containing proliferated connective tissue which appears to originate in the interlobular triangles, in which the tissue is loosened and freely infiltrated with round cells. Especially noticeable are numerous longer and shorter cellular cords, cut longitudinally, transversely, and obliquely, and undoubtedly made up of epithelial cells whose nuclei stain readily. Sometimes there is a distinct though narrow lumen in the cell masses. Undoubtedly it concerns proliferation of the interlobular bile passages, which is the result of a form of regeneration of the finer biliary ducts that underwent disintegration. In the outskirts of these areas of young connective tissue are also often found small insular districts of coherent liver cells proper, manifestly the result of proliferation in occasional surviving hepatic cells. It is not yet clear whether this regenerative process may go on to the extent that the organ resumes its functions and life is maintained. [Marwedel ("Ziegler's Beiträge," 1895, xvii, 143-205) and Mar-

PLATE 63.

FIG. 1.—Acute Yellow Atrophy of the Liver with Hemorrhages. $\times 100$. The normal structure of the liver almost wholly destroyed. In place of the cords of liver cells is a coarse meshwork with hemorrhagic foci. Nuclei of liver cells in part disintegrated; nuclei of vascular epithelium intact.

FIG. 2.—Proliferation of Bile Ducts in Acute Yellow Atrophy. $\times 80$. 1, The tissue almost wholly degenerated into fat and densely occupied by vacuoles; 2, young connective tissue with numerous longer and shorter portions of narrow epithelial canals (newly formed biliary ducts) interspersed with small islands of surviving or regenerated hepatic tissue.

chand (*Ibid.*, 206–219) describe the regenerative changes in acute yellow atrophy, which in rare cases may be followed by recovery.] Proliferations of bile ducts are frequent also in other destructive processes in the liver (see under Cirrhosis).

The fat content of the liver is greatly increased in acute yellow atrophy, and at the expense of fat-free dried residue, so that the fat must be assumed to form degeneration of the proteids of the liver cell. The analyses of Perls and v. Starck show:

	WATER.	FAT.	FAT-FREE DRY RESIDUE.
Normal liver,	76.1	3.0	20.9
Acute atrophy, { Perls,	87.6	8.7	9.7
{ Perls,	76.9	7.6	15.5
{ v. Starck,	80.5	4.2	15.3
Phosphorus-poisoning (v. Starck), . .	60.0	29.8	10.0
Acute fatty degeneration (v. Starck),	64.0	25.0	11.0

FATTY LIVER.

The amount of fat in the normal liver varies, in accord with the general corpulence of the individual, from about 1.8 to 5%. Under pathologic conditions the amount of fat may increase enormously, even to 40% and above. Abnormal accumulations of fat in the liver are designated

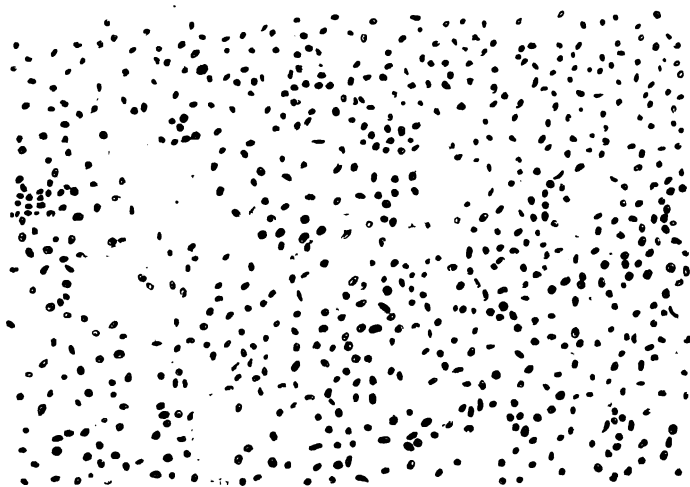


Fig. I.

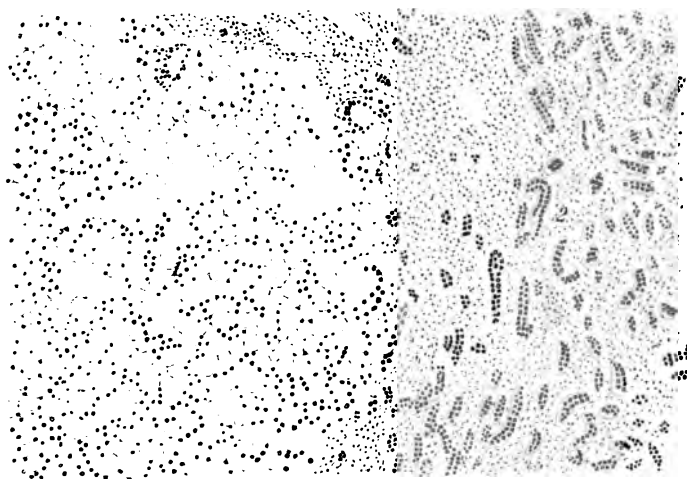
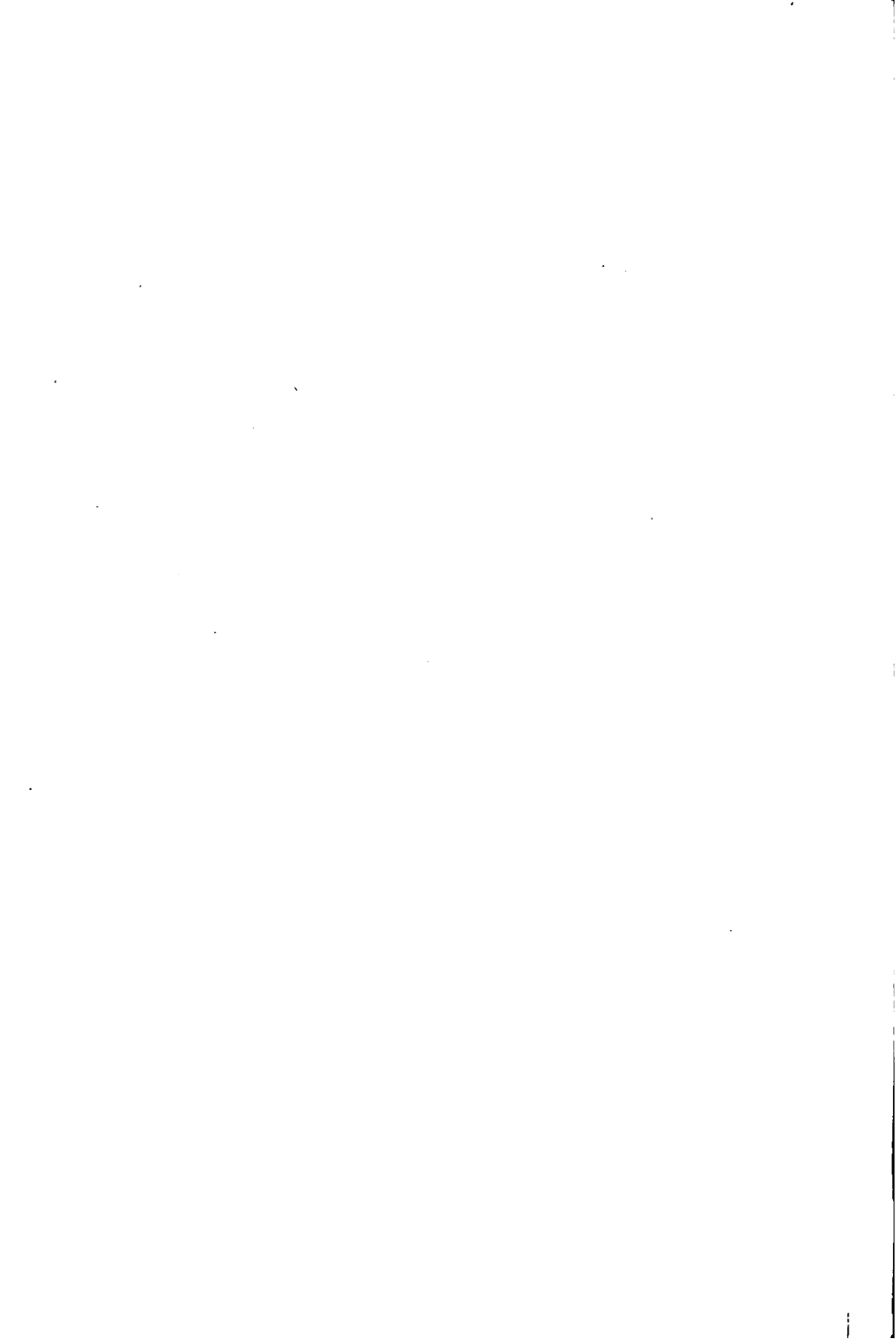


Fig. II.



as fatty liver. Fatty liver may arise in various ways: from increased ingestion of fat; by deposition of fat from other parts of the body, more particularly the *paniculus adiposus*; and by disintegration and transformation into fat of the proteids of the liver cells themselves. In the two former instances the liver cells are found uniformly well preserved, there being only an increased deposition of fat, but in the last case there is a real disintegration of the cellular elements and diminution of the protoplasm. Neither process, however, often occurs in pure form. In all degenerative changes that lead to the formation of fat there is always also an increased fatty infiltration of the liver tissue, and, reversely, higher grades of infiltration are always associated with destruction of cells. Here we have the reason why a sharp line of distinction cannot be drawn between fatty infiltration and fatty degeneration, and why they are considered together.

The etiology of fatty liver is dependent on various factors. Continuous ingestion of food rich in fats and carbohydrates leads to typical fatty liver, as shown experimentally by the fattening of animals for slaughter ("Strassburger goose liver"). In many persons there exists a special disposition to an increased general deposition of fat (adiposity), even when the food is not especially rich in fats, and in this process the liver partakes to a marked degree. All conditions that reduce the oxidative processes in the body favor abnormal accumulation of fat in the liver, especially the diseases that reduce the amount of hemoglobin (anemia, chlorosis, leukemia, pernicious anemia). The fatty liver of the phthisical has been referred to deficient oxidation on account of reduction in the respiratory surface of the lungs. Local fatty infiltration and degeneration may result from circulatory disturbances (passive congestion and nutmeg liver), and for the same reasons in the vicinity of tumors and new productions (carcinoma, echinococcus cyst), and also of tubercles and syphilitic growths.

PLATE 64.

FIG. 1.—**Cloudy Swelling of the Liver in Sepsis.** Fresh teased preparation. $\times 300$. The single, easily isolated liver cells are greatly enlarged, rounded, in part ballooned. The protoplasm is filled with numerous, very fine, grayish granules. At 1 is a swollen star-shaped cell of Kupffer.

FIG. 2.—**Acute Yellow Atrophy of the Liver.** Fresh teased preparation. $\times 300$. Advanced disintegration and fatty degeneration of the liver cells. The individual cells are large and vesicular, filled with fat particles of various sizes and with yellow granules of biliary pigment. The nuclei are mostly obscured. There are free-fat droplets from the bursting of liver cells.

FIG. 3.—**Senile Brown Atrophy of the Liver.** $\times 64$. More acini than normally are seen in one field because they are smaller. 1, Vena centralis cut transversely; 2, central zone of acinus filled with brown pigment; 3, peripheral, non-pigmented zone.

Furthermore, there are a number of intoxications that lead to an increased deposition of fat in the liver, often to an enormous extent. This effect may be explained either as the result of a direct injury and disintegration of liver cells or as due to changes in the composition of the blood and consecutive disturbances of oxidation. Acute phosphorus-poisoning is the most striking example of this kind. As early as a few hours after the taking of this substance the liver cells become so filled with fat droplets that the cell contours and nuclei appear absent, but they are rendered easily distinct again by extraction of the fat. A similar action is produced by arsenic, antimony, copper, mercury, and aluminum; by mineral acids; and, further, by carbonic oxid, petroleum, chloroform, bromethyl, iodoform, nitrous oxid, carbolic acid, phloridzin, ricin and abrin, chronic morphinismus, poisonous fungi (*Agaricus muscarius*), poisonous meats and fish, and decayed maize (in pellagra) (Hoppe-Seyler). Chronic alcoholism also favors deposition of fat, and, in addition to the cirrhotic hepatic processes, alcoholics commonly present increased fatty infiltration of the liver. In all infectious diseases



Fig. 1.

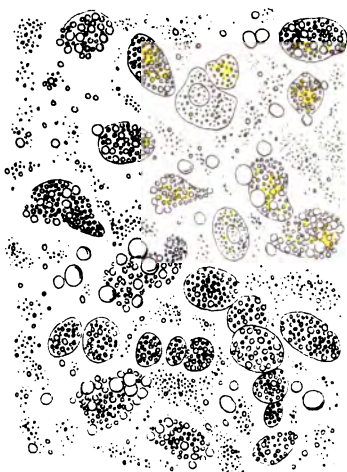


Fig. 2.

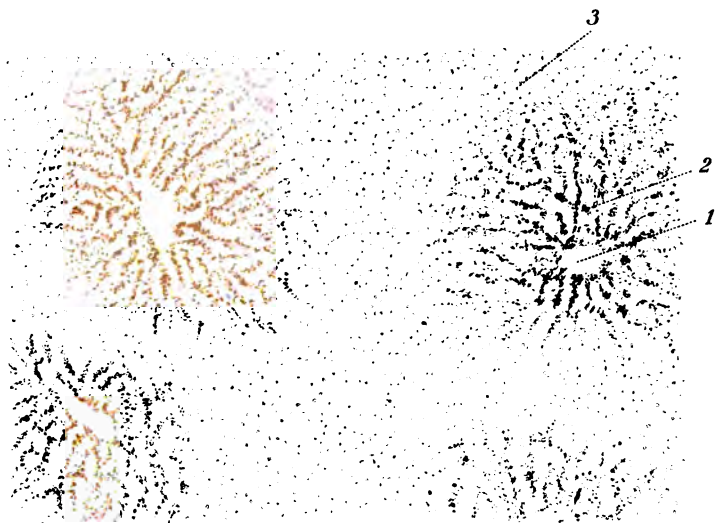


Fig. 3.



prolongation of cloudy swelling may lead to genuine fatty liver.

The fatty liver of the phthisical and other cachectic patients is probably the result of an infiltration with fat from other parts of the body, especially from the subcutaneous tissue, which is absorbed under the wasting influence of certain diseases.

Deposition of fat in the liver does not take place uniformly and diffusely. The peripheral parts of the lobules are affected first, probably because the exciting agents reach the liver through the hepatic artery.

Frozen sections of fatty livers, examined preferably fresh, show the centers of the lobules surrounded by dark rings or polygonal meshes composed of glistening fat globules. Larger accumulations of fat are found more particularly about the triangular area of fibrous tissue surrounding the larger portal branches, hepatic arteries, and bile ducts. In this district the liver cells often seem to have disappeared wholly, having been replaced by fat. On treating such sections with fat solvents (alcohol, ether, paraffin embedding) the nuclei and the cell bodies become distinct again, the latter being filled with innumerable vacuoles. In place of the fat globules are rounded openings, which give to the section a more or less pronounced sieve-like appearance. The fat globules vary in size. Small droplets are present normally in the protoplasm of the peripheral parts of the lobules, especially in well-nourished persons, and under pathologic conditions they may become very numerous and run together in single drops which fill the whole cell. Naturally, this leads to an increase in the size of the cells, of the cellular columns of the lobules, and thus of the whole organ. Often the fat drops are not round, but irregularly notched, or of curved outline. By means of suitable methods a membrane is demonstrable, similar to that around milk globules, and mostly consisting of albumin.

In the more severe degrees of fatty liver the deposition

PLATE 65.

FIG. 1.—Amyloid Liver. $\times 98$. (Hematoxylin-eosin.) 1, Central vein. Portal capillaries surrounded by homogeneous masses and bands; the epithelial lining distinct. Columns of liver cells compressed to narrow, atrophic strips.

FIG. 2.—Advanced Amyloid Degeneration of Liver. $\times 67$. (Picrocarmin.) By confluence of the amyloid material the columns of liver cells have been wholly replaced (upper right corner); elsewhere they are greatly shrunken, the lobular structure obliterated.

of fat droplets advances toward the centers of the acini, and in extreme cases all the zones may be infiltrated in equal degree. While the lobular markings in the early stages are rendered more distinct, because the fatty peripheral zone is yellow and prominent and the central zone red and depressed, this distinction in the later stages gives way to a diffuse, lemon-yellow coloration. The increasing swelling of the liver-cells results in compression of the capillary blood-vessels, and the whole liver becomes uniformly anemic. In acute phosphorus-poisoning the fatty changes rapidly traverse all the zones of the acini, and great distention of the cells with fat globules causes cell disintegration ("fatty degeneration").

At the same time other changes become manifest: At certain points, especially around the portal veins, but also around the intralobular and sublobular veins, single cells or groups of cells become necrotic, the nuclei disappear or the chromatin is compressed into clumps ("pyknosis"). The cell bodies are either homogeneous, scaly, or broken up into irregular, minute, lighter and darker particles. Often extravasation of red corpuscles takes place about these areas, and many red corpuscles may be found within liver cells, and even in those that show no other changes. Many hepatic cells contain rounded, oval, and also vacuolated bodies, usually somewhat smaller than the nuclei of the cells, generally single, but sometimes in large numbers. These are the so-called "Russell's bodies," which probably



Fig. 1.

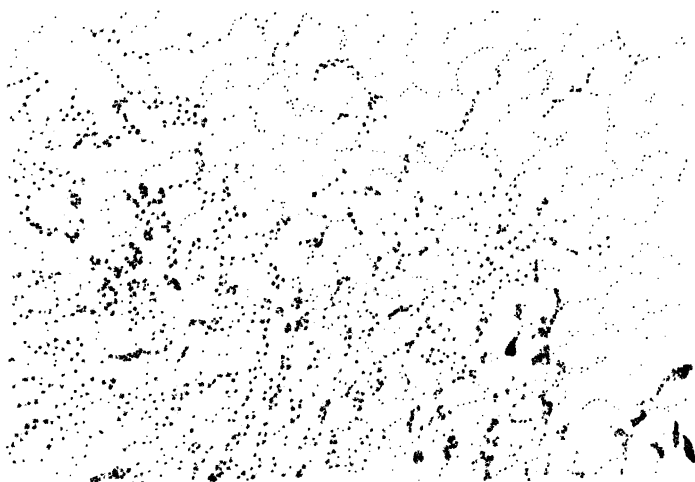


Fig. 2.

are derived from included leukocytes and also from condensed red corpuscles. Often other intracellular bodies are present, such as larger concentric bodies, similar to myelinic masses, probably the result of a kind of saponification produced by the action of the protoplasm upon the fat globules within the cell (Quincke). Biliary pigment usually occurs in but very minute quantities in simple fatty livers.

ATROPHY, GLYCOGENIC INFILTRATION, AND ANTHRACOSIS OF THE LIVER.

Atrophy of the liver tissue takes place either diffusely or in a circumscribed form. Circumscribed atrophy is shown well in the so-called lacing liver, in the resulting furrow (often also in the pendulous part of the right lobe below the furrow), in the vicinity of tumors of all kinds, in chronic passive congestion, and in cirrhosis. General atrophy occurs commonly as the result of senile involution, and, furthermore, in severe cachexias and in marasmus.

Microscopically there is demonstrable a distinct diminution of the liver cells and of the lobules. In a frozen section, for example, a larger number of acini than normal appears in the field under a low power, and the venæ centrales seem nearer to one another, as do also the connective-tissue triangles about the portal, hepatic, and biliary canals, so that at first sight it looks as if the organ contains more connective tissue than normal. It is not a real, but mostly only a relative, increase of connective tissue. Higher magnification and thinner stained sections show most clearly diminution of the volume of the individual liver cells, especially in the central parts of the lobules. The cells are peculiarly angular in form, the nuclei diminished in size, the chromatin somewhat condensed. The cells also contain large masses of a finely granular, yellowish-brown, iron-free pigment. The cords of shrunken pigmented cells radiate toward the circumference of the

PLATE 66.

FIG. 1.—Atrophic Cirrhosis of the Liver. $\times 40$. Well-marked bands of connective tissue (2) divide the parenchyma of the liver into irregular islands of varying size; even in the larger of these there is no division into lobules (1). Vena centralis absent in some places; in others, excentric (upper right corner). 3, Smaller islands of liver cells. Scattered heaps of round cells in the connective tissue, and toward the left a few epithelial canals with darkly colored nuclei (newly formed bile ducts).

FIG. 2.—Atrophic Cirrhosis with Fatty Infiltration (So-called Fatty Cirrhosis). $\times 40$. Frozen section. 1, Islands of liver cells with disarrangement of lobular structure; 2, infiltration of fat in the cells; 3, long fibrillæ of connective tissue sharply circumscribed; 4, biliary pigment.

lobules, but only in the severest forms of atrophy is the whole lobule involved (atrophia fusca hepatis, brown atrophy of the liver). Notwithstanding the narrowness of the cell cords, the capillaries are not dilated, but generally rather narrow, the amount of blood being small. In the peripheral parts of the acini the liver cells gradually present the normal size and form. In advanced instances the structural details of the centers of the lobules may be lost through cellular disintegration and formation of granules. The pigment, which probably is not derived from the blood, but from the proteids of the cells, is of the same nature as similar pigment in atrophy of other organs, such as the heart, the intestines, the kidneys, the voluntary muscles. It should not be confounded with biliary pigment.

The macroscopic appearances—namely, diminution of the whole organ and deep brown coloring of the cut surface—are explained by what has been said. The shrinking of the lobules is often recognizable macroscopically or by means of a lens of low power, the centers being generally depressed, and the consistence of the organ slightly increased.

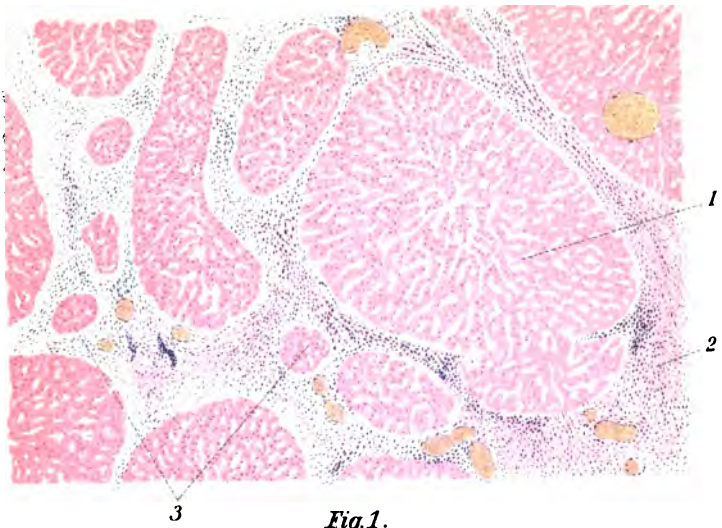


Fig. 1.

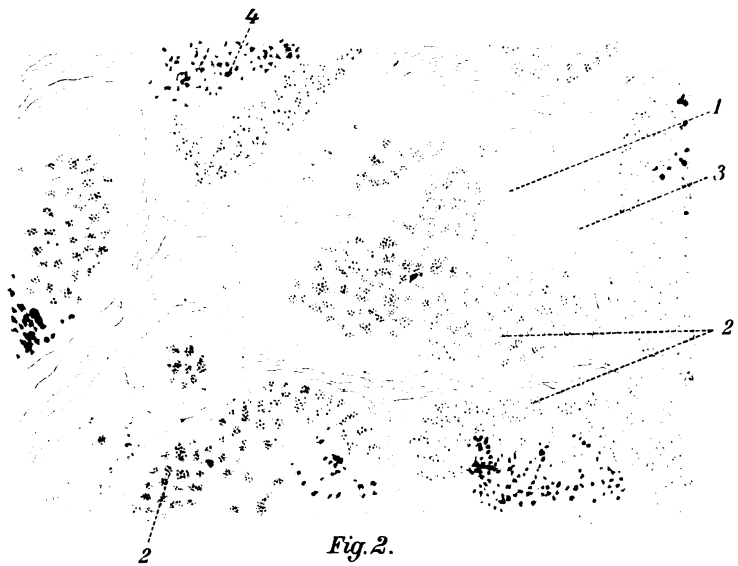


Fig. 2.



In diabetics a deposition of glycogen in larger and smaller granules occasionally occurs, especially in the peripheral parts of the lobules. Glycogen is best demonstrated by placing fresh sections of pieces hardened for a short time in absolute alcohol in iodine dissolved in mucilage, when the balls and scales are colored brownish-red.

In older persons with marked anthracosis of the lungs and lymph glands coal-dust is often found in the liver (anthracosis hepatis), the coal-dust having been brought to the liver by way of the blood-vessels (see Anthracosis of the Lungs, vol. I). [Welch has described anthracotic cirrhosis of the liver caused apparently by the irritation of the particles of soot.] The liver cells are not directly involved, as the coal-dust is deposited between the cells in the central parts of the lobules, where the pigment often lies in triangular or irregular heaps, due to inclusion in Kupffer's cells; or the pigment lies in the interacinous connective tissue, being probably first deposited in the cells lining the lymph channels. Frequently this exogenous pigmentation is associated with brown atrophy of the liver in senile individuals, the black heaps of soot standing out clearly from the brown liver cells.

AMYLOID LIVER.

Amyloid degeneration of the liver is a retrogressive process that probably never is isolated, but accompanied by some degeneration in other organs, such as the spleen, kidneys, intestines. The etiology is that of general amyloid degeneration (see the volume on "General Pathologic Histology"). As in other organs, amyloid degeneration of the liver also takes its starting-point from the blood-vessels, and more particularly from the portal capillaries in the intermediary zone, so that the initial stage, not definitely recognizable with the naked eye, may be studied here under the microscope. Homogeneous, glassy masses and bands form in the capillary walls external to the epithelium,

PLATE 67.

FIG. 1.—(Hypertrophic) Diffuse Cirrhosis of the Liver. $\times 160$. Lobular marking lost, the liver tissue separated into narrow strands by proliferating young connective tissue with short fibers, in which are wide capillaries with distinct epithelium.

FIG. 2.—Diffuse Cirrhosis of the Liver (Hypertrophic Cirrhosis) with Proliferation of Bile Ducts. $\times 160$. The liver tissue consists of small masses of cells widely separated by proliferated connective tissue. Below, the connective tissue is more dense; round-cell infiltration about a blood-vessel; in the connective tissue newly formed biliary ducts [1].

and eventually complete cylinders form about the capillary lumen and gradually extend centrally and peripherally at the same time as their diameter increases. The lumens generally remain patent for a long time, and it is noteworthy that the epithelium remains distinct even in advanced stages. The material gives the familiar reactions with iodine and with iodine and sulphuric acid, and shows metachromatism with certain aniline substances (see the volume on "General Pathologic Histology").

Under the influence of the increasing thickness of the amyloid bands the adjacent cords of liver cells become more and more compressed and narrowed until they form but thin strands, and eventually they may disappear

PLATE 68.

FIG. 1.—Hypertrophic Cirrhosis of the Liver with Proliferation of Bile Ducts. $\times 270$. At the upper left corner hypertrophic liver cells with tubular arrangement and occasional multinuclear cells. In the recent, cellular connective tissue large epithelial cells arranged in the form of cylindrical canals (formation of bile ducts from liver cells).

FIG. 2.—Multiple Circumscribed Necroses in the Liver in Puerperal Eclampsia. $\times 75$. In the normal liver tissue (1) are sharply circumscribed districts (2) with swollen liver cells, the nuclei of which are not stained, only the nuclei of the epithelium of the capillaries being intact.

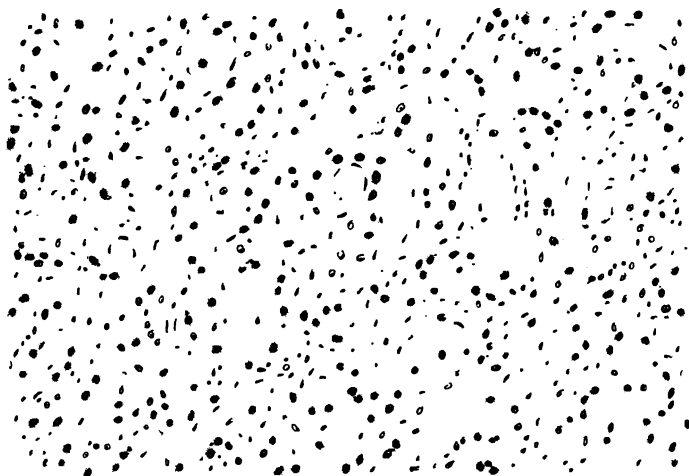


Fig. 1.



Fig. 2.

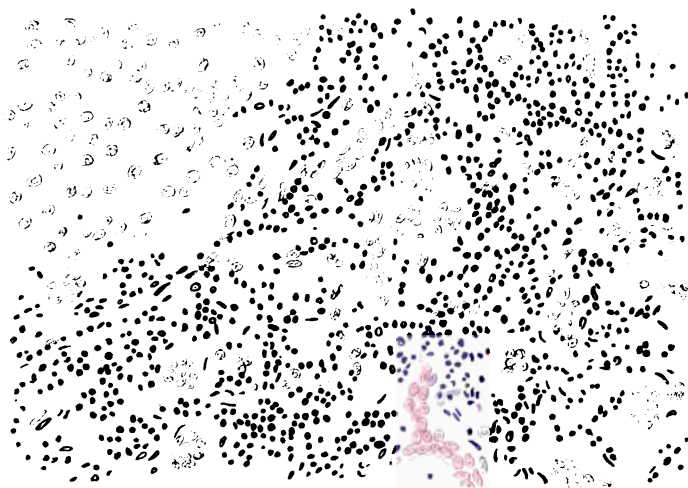


Fig. 1.

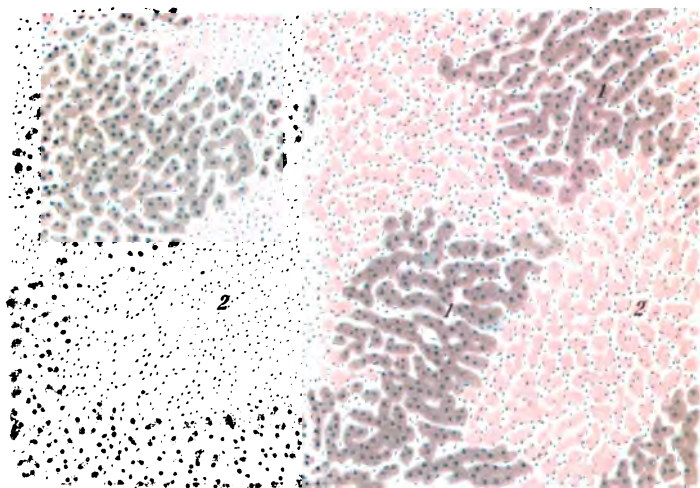
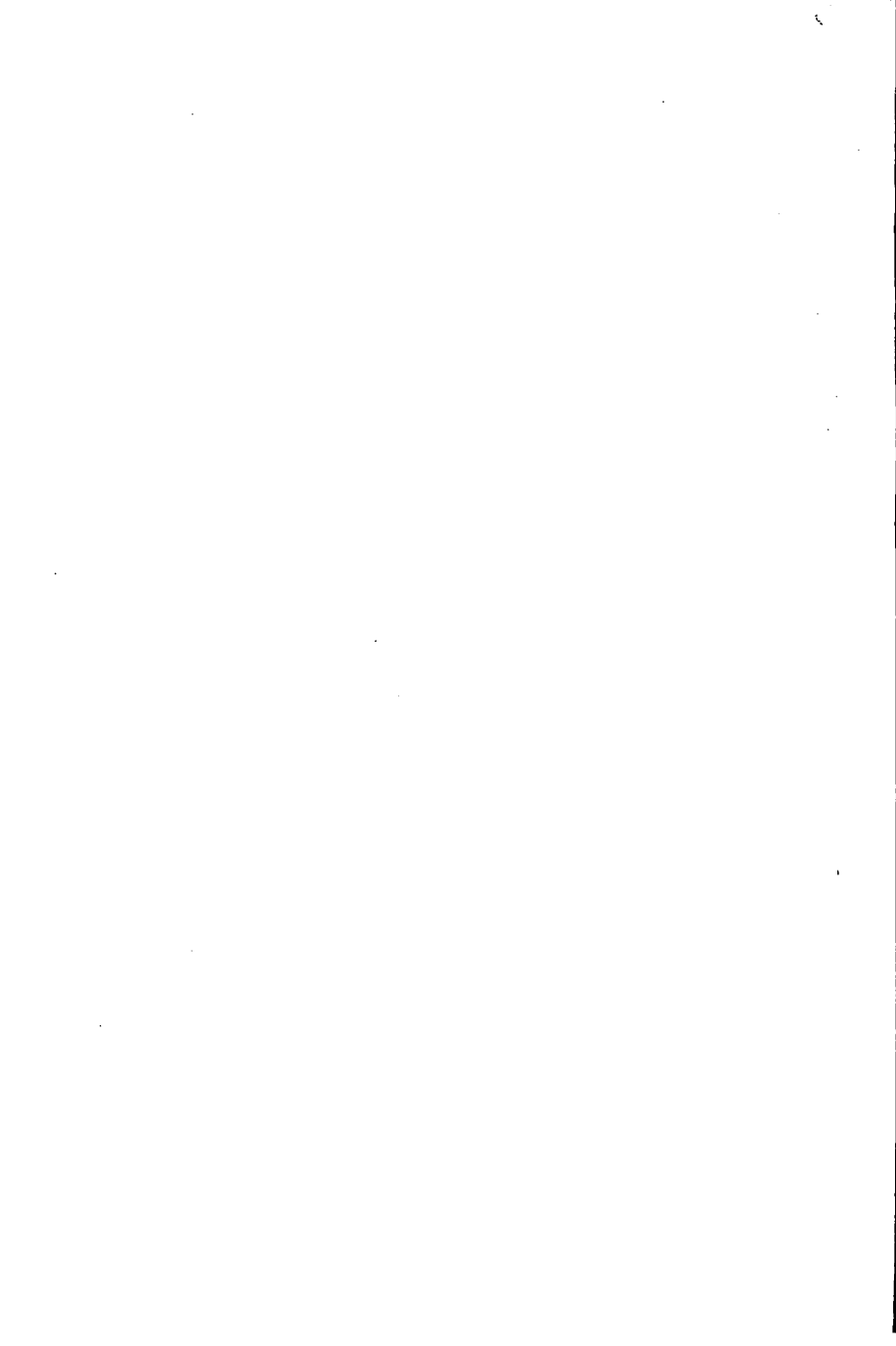


Fig. 2.



wholly. Following the localization of the degeneration, this atrophy occurs first in the middle zones of the acini; thus the continuity of the rows of cells is broken, and, as the process extends, irregular islands of parenchymatous cells are formed centrally and peripherally. These islands generally show a marked fatty infiltration. As the liver cells perish the amyloid material coalesces into larger flakes, perforated by fine spaces representing the capillary lumens. The smaller hepatic arteries and the interacinous portal branches become involved later in the process. In no case is there amyloid degeneration of the liver cells proper; these perish from pressure atrophy.

The formation of amyloid flakes between the cords of liver cells, and their continued increase, lead to enlargement of the liver, and the physical nature of the amyloid substance explains the increased consistency and the glistening, lardaceous appearance of the cut surface. The progressive narrowing of the vessels of the liver renders it highly anemic.

ICTERUS.

If the outflow of the normal secretion of the liver, the bile, into the intestine is hindered mechanically, then a resorption of the constituents of the bile leads to biliary pigmentation of the liver, and by transportation through the blood a biliary imbibition of the whole body may result. This, the most frequent form of icterus, is known as resorptive, mechanical, or obstructive icterus. There is another genesis of icterus: through disease of the liver cells the bile may not reach the biliary ducts, but some of it may pass toward the blood-vessels and be stored in the liver itself. This has been called parapedesis of the bile (Minkowski), diffusion icterus, or akathectic icterus (*καθέξειν*, "hold fast") (Liebermeister). E. Pick has called it paracholia.

The microscopic appearance of the icteric liver varies according as the duration and intensity of the biliary ob-

PLATE 69.

FIG. 1.—The Liver in Leukemia (Leukemic Infiltration). × 80. 1, Vena centralis ; numerous lymphocytes in the portal capillaries between the columns of liver cells ; 2, periportal connective tissue infiltrated with radiating groups of lymphocytes.

FIG. 2.—Mycotic, Suppurative Embolic Thrombosis of Portal Vein (Mycotic Pylethrombophlebitis). × 80. 1, Wall of a large branch of the portal vein, infiltration in periportal tissue ; 2, liver tissue, compressed and somewhat concentric cellular columns ; 3, necrotic zone ; 4, pus corpuscles ; 5, heaps of micrococci (staphylococci).

struction vary. In the earlier stages the liver cells proper are free from biliary pigment, which is accumulated in the bile ducts. The interlobular passages become dilated, and the ectasia extends to the intralobular bile capillaries, which are filled as if injected with yellowish-green, cylindrical, sausage-shaped, and often branching masses (best seen in thin frozen sections of the fresh tissue). Often a club-shaped process may be followed from the bile capillaries into liver cells, ending in a so-called secretory vacuole. The connective-tissue cells in the neighborhood of the larger bile ducts appear pigmented, and finally bile pigment accumulates in the liver cells. Here again is observed a typical localization, as the central parts of the lobules are first affected by light-yellow pigmentation. Cross-sections of the lobules show about the central vein neat little heaps of pigment, often star-shaped, sending processes outward to the periphery. Severe obstruction causes pigmentation of the lymphatic and vascular epithelium, the cells of which swell up and project into the lumen.

Gmelin's test for biliary pigment (bilirubin) may be applied to fresh sections: Potassic hydrate is allowed to run in under the cover-glass; after a short time it is washed away with water, and then strong nitric acid containing some nitrite is added. The pigment granules now pass through various colors—green, blue, violet to red.

In long-continued biliary obstruction necrotic foci develop in the liver. These may be produced experiment-

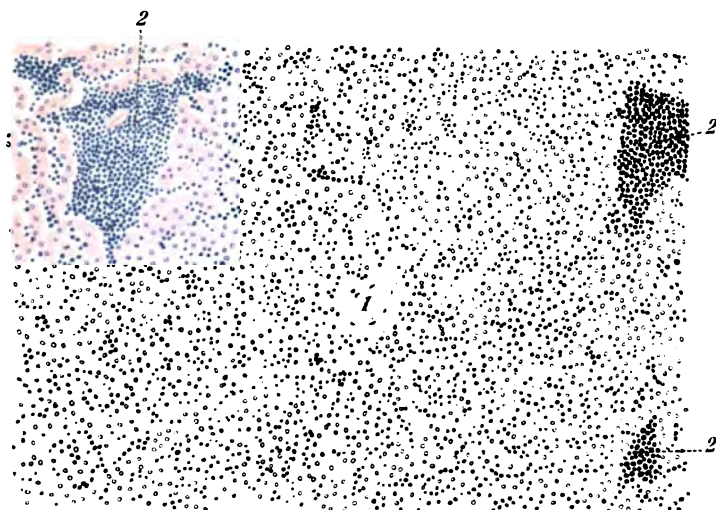


Fig. 1.

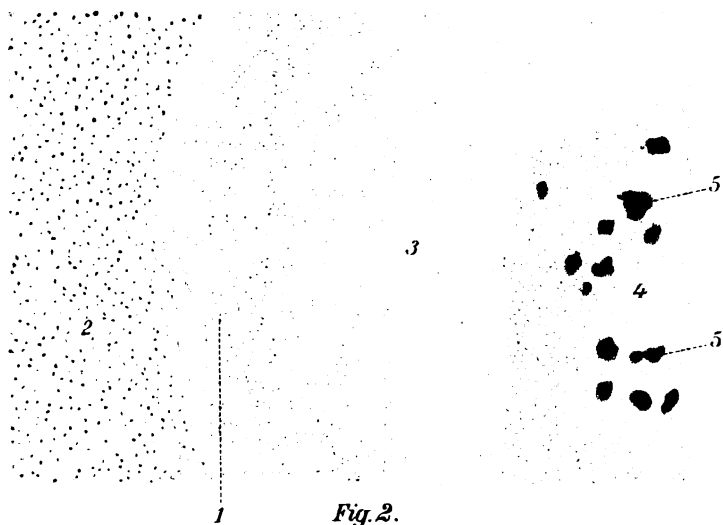
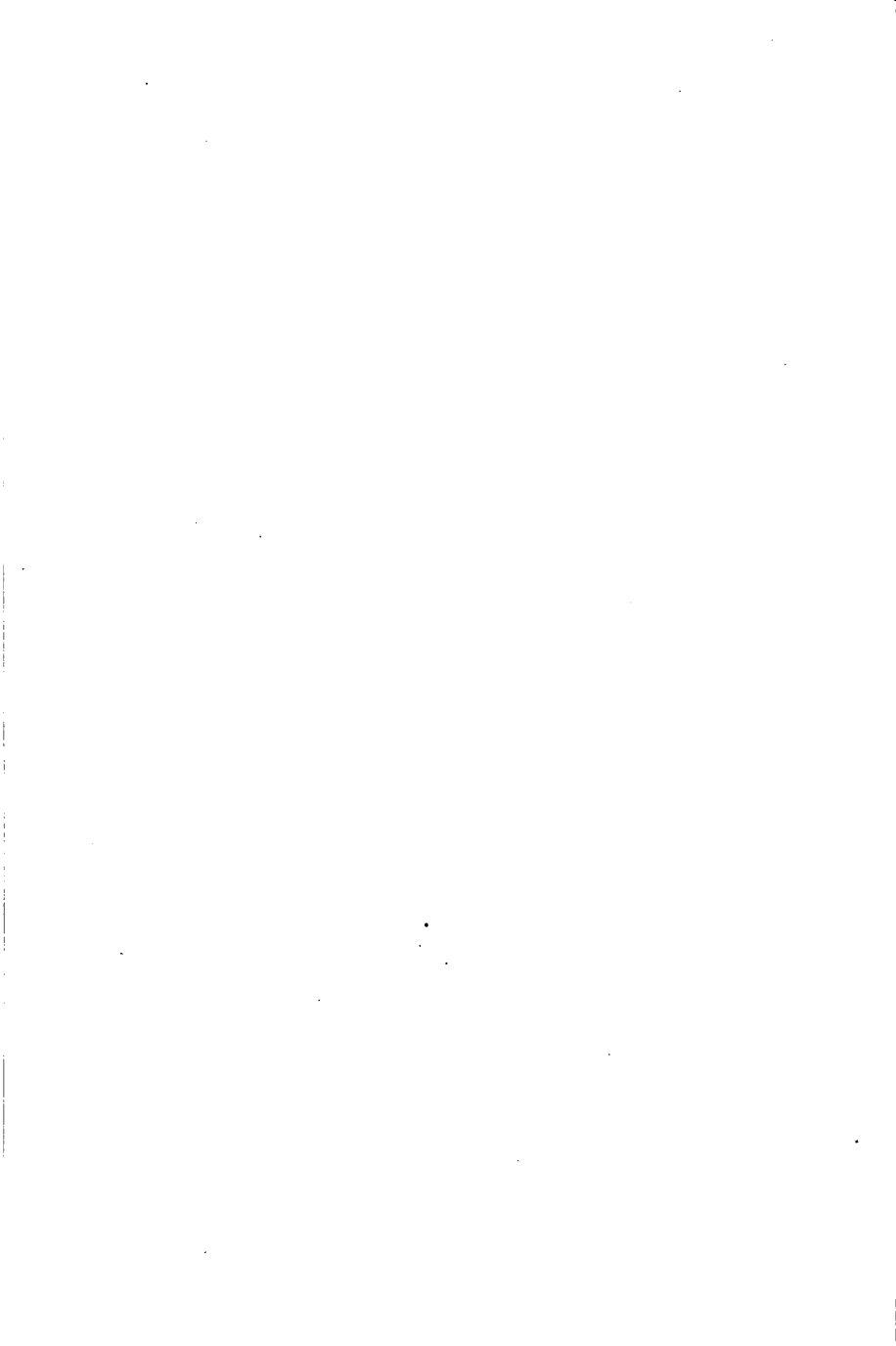


Fig. 2.



ally by ligation of the bile duct. The smallest foci include only a few liver cells; the largest may involve several lobules. The cells in the foci are icteric, swollen, hyaline, and vacuolated. The nuclei, and later the protoplasm, lose their affinity for stains. Often round cells accumulate about the foci, a cellular and later fibrous connective tissue springs up, and the necrotic parts are absorbed (Gerhardt). The interlobular ducts show desquamation and proliferation of the cells ("catarrh"), and bud-like evaginations lined with a low flat epithelium may form, while the surrounding connective tissue proliferates (Charcot's "biliary cirrhosis"). Frequently chronic icterus of the liver in man is complicated by secondary inflammatory changes initiated by intestinal micro-organisms that have entered the bile ducts. [For a recent and comprehensive study of obstructive biliary cirrhosis see article by W. W. Ford, "Amer. Jour. Med. Sci.," 1901, cxxi, 60-84.]

CIRRHOSIS OF THE LIVER.

By cirrhosis of the liver is generally meant all forms of intrahepatic connective-tissue proliferation that lead to more or less deformation of the organ. The development of connective tissue in this way is empirically regarded as the result of chronic inflammatory processes in the pre-existing stroma (the normal interstitial tissue), and on this account every process of this kind in the liver is also designated as "chronic interstitial (productive) hepatitis." But it must be remembered that the development of cirrhosis does not depend in every case upon primarily inflammatory processes starting in the interstitial tissue. The views are still divided, even at the present day, as to the part played by primary degenerations in the parenchyma of the liver in the various forms of cirrhosis. In connection with "fatty liver" it was pointed out that in chronic phosphorus-poisoning the broken-up liver parenchyma in part may be replaced by connective tissue, and

PLATE 70.

FIG. 1.—**Miliary Tuberculosis of the Liver.** $\times 70$. Two foci, consisting of smaller confluent tubercles, which are still distinguishable. The giant cells are rounded. The foci are situated in the periportal tissue in the vicinity of a portal branch.

FIG. 2.—**Tuberculous Cholangitis (Tuberculous Periangiocholitis).** $\times 63$. 1, Epithelium of a larger bile duct; 2, adjacent, fattily infiltrated liver tissue; 3, caseous center of a large tuberculous focus at the margin of which the confluence of smaller nodules is still visible; 4, perforation into the lumen of the duct, which contains caseous masses and flakes of biliary pigment.

such is also the case in acute yellow atrophy, as well as in a number of slowly progressive intoxications.

It is generally believed that certain chronic intoxications (alcohol) and infections (syphilis, malaria) are of great significance in the etiology of cirrhosis of the liver, at least in the majority of the forms; and it would seem that there is considerable evidence for the opinion, which is gaining ground of recent years, namely, that cirrhosis of the liver is a "chronic focal, recidivous, degenerative process." In all cases the characteristic feature, in addition to the simple degenerative processes, is the formation of new connective tissue. The latter may vary in extent and localization even in the single case.

Formerly the distribution of the connective tissue was regarded as quite simple, and as following two principal routes. This view is still to some extent in vogue, although it has frequently been shown to be false. It was thought that the connective tissue either developed around the single lobules, pressing them apart, and later concentrically constricting the lobules ("interlobular cirrhosis"), or that the connective tissue penetrated into the lobules, separating the cellular cords and even the single cells ("intralobular cirrhosis"). Even the macroscopic appearances of the cirrhotic process were regarded as depending upon the distribution of the connective tissue, it being held that the

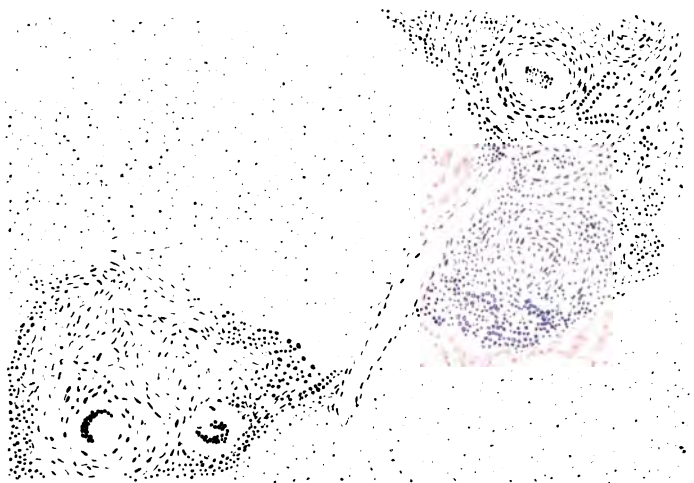


Fig. 1.

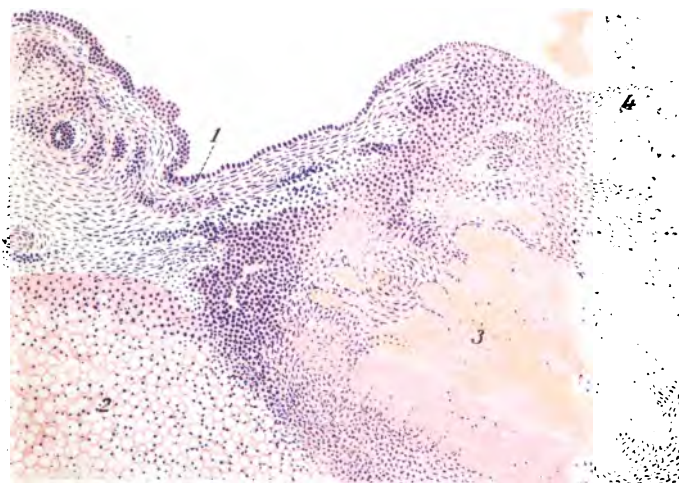


Fig. 2.

cirrhosis accompanied with diminution of the liver—"atrophic cirrhosis"—was in the main an interacinous process, while cirrhosis with enlargement of the liver—"hypertrophic cirrhosis"—depended upon an intralobular development of connective tissue. But closer study of the histologic details has shown that these views are not adequate; for the distribution of connective tissue is not so simple and regular as appears at first sight, and, on the other hand, it is found that the islands of parenchymatous tissue, which formerly were regarded as persisting or compressed liver lobules, very often are secondary formations of a regenerative nature.

So long as the etiology and pathogenesis of the different forms of cirrhosis of the liver are not clearly understood, practical reasons demand some classification of the cirrhotoses based partly upon macroscopic, partly upon microscopic, distinctions. It must be borne in mind, however, that fundamental histologic criteria, of value from the point of differential diagnosis, do not exist. The inspection of a single section, and even of many sections from the same case, may be utterly inadequate to furnish the information necessary in order to determine the precise form of cirrhosis present, because the different forms of cirrhosis present such marked variability within a single liver, and even within the single liver lobule, passing into and overlapping one another.

All processes that cause degenerations and all that cause chronic inflammations in the liver may lead to the picture of cirrhosis. In the former instance it is produced by fibrous replacement of the resulting defect, in the latter by transformation of the granulation tissue in the interstitial framework into fibrillar connective tissue.

Having this in view, the polymorphism of the macroscopic and microscopic manifestations of cirrhosis of the liver becomes intelligible.

Probably the most frequent form is the one in which considerable diminution, nearly uniform shrinking, and

PLATE 71.

FIG. 1.—Recent Gummous Hepatitis in Acquired Syphilis.
Two miliary nodules with caseous centers and fibrous margins; the adjacent liver tissue infiltrated with round cells.

FIG. 2.—Large Calcified Gummas of Liver with Secondary Syphilitic Cirrhosis. $\times 30$. 1, Small persisting islands of liver cells, surrounded by a very dense fibrous tissue (2) with numerous vessels (3), the walls of which are thickened and the lumens nearly closed by enarteritic proliferation; 4, large caseous area surrounded by a ring of calcareous incrustation.

increased consistency are associated with an irregular, partly coarse, partly fine granulation of the external and of the cut surfaces. The cut surface shows numerous, larger and smaller, internally often yellow projections within the spaces of a retracted, grayish-white network with meshes of varying size. (This has been erroneously described as "lobular" marking; Kaufmann's "pseudo-lobular" marking.) This is Laennec's cirrhosis of the liver (*καθ' ἐξοχὴν*), now commonly called atrophic cirrhosis, granular atrophy, granular contracted liver [hob-nailed cirrhosis, gin-drinker's liver], and, after its discoverer, Laennec's cirrhosis.

The study of a fresh frozen section with a low power will throw light upon the nature of the changes (Plate 66, Fig. 2). There is seen plainly a lighter grayish network of long connective-tissue fibrillæ, which form variously sized spaces containing masses of liver cells. The liver cells are usually charged with glistening fat drops and fine heaps of light yellow and brownish bile pigment; both these substances, however, being distributed irregularly.

Closer study of stained sections shows that the islands of parenchymatous tissue do not correspond to lobules surrounded by fibrous elements, as seen, for instance, in the liver of swine, but that the central veins, which are so important for the recognition of the lobular structure, are fewer than usual, and that their relations to the cell columns

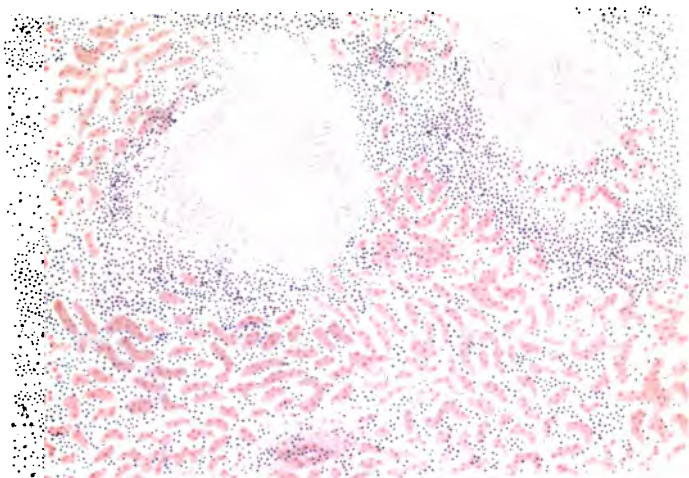


Fig. 1.

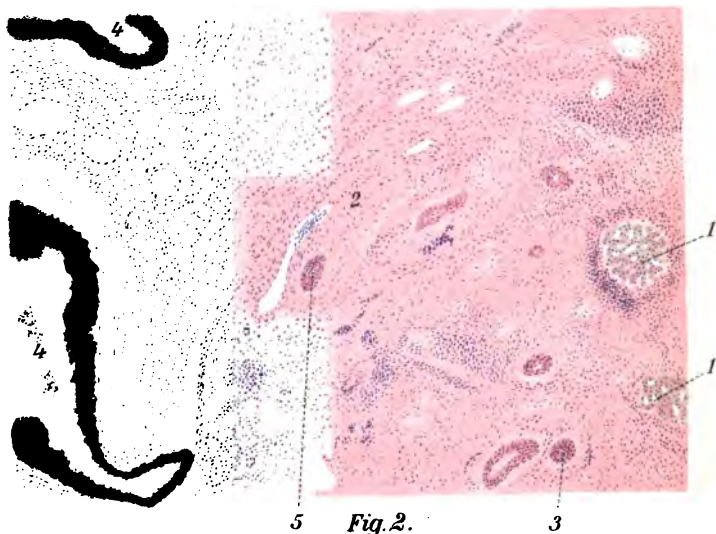
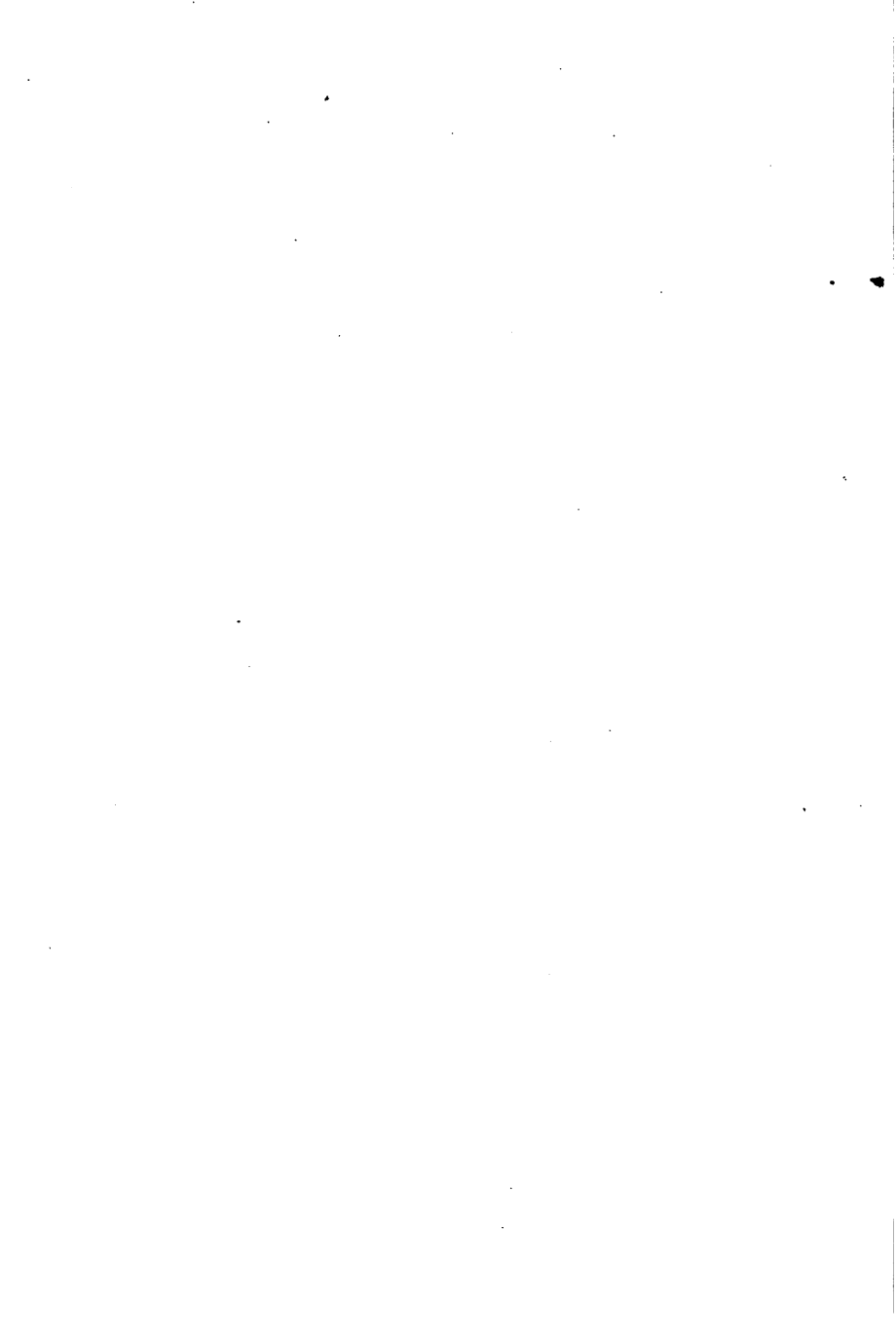


Fig. 2.



are atypical. The cell columns are pressed out of the regular radial order and rearranged in the form of a network with fine, rather long capillary spaces (Plate 66, Fig. 1). Not infrequently a continuous series of sections of an island of liver parenchyma inclosed by fibrous tissue fails to disclose a single central vein. In other instances the vein may be excentric (Plate 66, Fig. 1, upper right corner); occasionally it lies near the periphery, in the margin of the connective-tissue; and in other parenchymatous districts there may be two or more central veins. The typical relations of the central vein to the portal capillaries and to the cellular cords are lost—a fundamental rearrangement of the entire structure of the liver has taken place (Kretz). It is not necessary to regard all the parenchymatous areas as “regenerated foci, springing from the relatively intact parenchyma,” although it is true that an extensive regeneration may take place in the isolated masses of liver cells inclosed by connective tissue, as shown by the relatively numerous mitoses in properly fixed preparations, and by the presence in single liver cells of many nuclei. And occasionally larger, macroscopically prominent nodules represent circumscribed hypertrophy of liver tissue, the so-called “liver adenomas,” which must not be confused with the “adenomas of the bile ducts” about to be mentioned. The liver adenoma often shows real multinuclear giant cells lying together in disproportionately small spaces.

In other places one frequently sees continued retrogressive changes in persistent masses of liver cells surrounded by connective tissue. The single cells show a high grade of fatty infiltration, and even complete degeneration; other cells are much shrunken and rounded, filled with icteric pigment, and with brownish granules, as in brown atrophy (p. 21).

It is quite evident that the granulations, and hence the cellular masses, which are identical, do not correspond to normal lobules. Consequently the connective-tissue pro-

liferation cannot be designated as interlobular. It takes place irregularly, now from the Glissonian tissue of the interlobular portal vessels, now in the vicinity of the central vein ("venous cirrhosis"), and now in both places at the same time ("bivenous cirrhosis"). This leads at one time to separation and constriction of a single lobule ("unilobular," "perilobular," "interacinous," "insular" cirrhosis), at other times several acini are surrounded and isolated from their connections ("multilobular" cirrhosis), and perhaps more frequently still the connective tissue extends irregularly into the parenchyma, disconnecting complexes of cells ("intraacinous" cirrhosis).

The common characteristic of the cirrhotic processes that lead to atrophy is this, that in the great majority of the cases continuous cell masses, parts of acini, whole acini, or groups of acini become surrounded by connective tissue.

In the so-called "hypertrophic cirrhosis," which Todd first pointed out as distinct and separate from Laennec's cirrhosis, and which is accompanied with a marked increase in the volume of the liver, progressive to the end, this separation of larger cell masses is usually absent in the beginning, although it does not constitute a constant and radical distinction applicable to each case. In this form the connective-tissue proliferation generally extends in a more diffuse manner between the rows of liver cells, surrounding very small groups of cells and even single cells ("monocellular" cirrhosis), which shrink gradually, and ultimately disappear from pressure atrophy. The lobular markings are wholly lost. Capillary blood-vessels are often present between the cells, and as the lumen is not closed, this is the usual explanation of the absence of ascites in hypertrophic cirrhosis (Plate 67, Fig. 1). The connective tissue does not usually assume the fibrillar and non-cellular character of atrophic cirrhosis, but is frequently infiltrated with round cells, especially in the vicinity of the vessels (Plate 67, Fig. 2).

All cirrhotic processes in the liver are characterized by

regenerative processes on the part of the biliary ducts, the so-called proliferation of bile ducts, which often is so prominent a feature in the microscopic picture. (It may be compared genetically with the atypical epithelial proliferations of the skin in connection with productive processes in the papillary body.) Very frequently the proliferated connective tissue contains epithelial tubules, which may have been cut transversely, obliquely, or longitudinally, and often are provided with a distinct though fine lumen (Plate 67, Fig. 2; Plate 68, Fig. 1). The single cells, with their deeply stained oval nuclei, which occur in regular order, are sharply distinguished from the rows of liver cells. Convolved tubules of this kind may occur uncut in the field, when several cells may be seen side by side. Ackerman was the first to show that these very fine canals may be injected from the hepatic duct, and that they consequently are in direct communication with the preexisting biliary passages. A part of them is evidently formed by buds from the interlobular ducts, the buds continuing to grow in length, while others are formed from single liver cells that have been severed from their normal connections, because the new ducts frequently pass to single liver cells or small groups of liver cells. This change of function of the liver cells, whereby the originally secretory gland cell changes into epithelium for the duct, becomes intelligible by recalling the phylogenetic development of the liver: in the amphibia and the reptilia the organ has a tubular structure, every bile duct being surrounded by circularly arranged hepatic epithelium.

Sometimes the proliferation of bile ducts assumes large proportions, so that the connective tissue contains twisted complexes of epithelial canals, the so-called "bile-duct adenoma." The newly formed connective tissue in more advanced stages usually contains very many elastic fibers, which occasionally and in spots exceed in number the collagenous fibers. It appears that the elastic fibers take their origin from the elastic elements in the adventitia of

the sublobular arteries and branches of the portal vein. [For the results of a recent study, by digestive and other late methods, of the elastic elements in cirrhosis of the liver, see Flexner, "Proc. Phila. Path. Soc.," 1901, iv, 9-17. From his study, and from investigations made by Oliver in my laboratory, it seems that the new elastic elements spring largely from the walls of the bile ducts.]

Injected preparations show that the vascularization of the new connective tissue largely takes place from the hepatic artery, whose capillaries often show an extraordinarily rich development, while the intertrabecular capillaries of the portal vein are occluded more and more, especially in the common forms of atrophic cirrhosis.

Special mention must be made of the "biliary cirrhosis" first described by Charcot and Gombault, reference to which was made under Icterus. This form of cirrhosis develops after occlusion and obliteration of the larger biliary ducts, and starts in the connective tissue about the affected ducts, where a diffuse proliferation is set up. Several factors are essential for its development, for it is usually absent after complete and lasting obturation of the hepatic duct by concrements, and it also fails to develop after strictly aseptic ligature of this duct (Dupré). [Cirrhosis develops if the animals are allowed to live long enough (Ford).] Evidently the development of pericholangitis as an early stage in biliary cirrhosis after incomplete obstruction of the bile ducts is especially favored by the entrance of micro-organisms from the intestinal canal. Experimentally, pericholangitis may be produced through ligation of the hepatic duct without complete exclusion of septic germs. [See Ford, "Obstructive Biliary Cirrhosis," "Amer. Jour. Med. Sci.," 1901, cxxi, 60-85.]

As pointed out under Icterus, circumscribed necroses in the parenchyma of the liver produced by biliary obstruction may be replaced by areas of connective tissue. A typical "biliary cirrhosis" is often found in the sheep in connection with the liver-fluke disease (distomatosis).

Pronounced fatty infiltration of the persisting parenchymatous areas, as may occur especially in atrophic cirrhosis, is spoken of as "cirrhotic fatty liver" [fatty cirrhosis] ("cirrhose grasseuse"). Occasionally cirrhosis may be associated with abnormal pigmentations, as in chronic malaria, in which the capillaries of the liver may be filled with a blackish pigment derived from the destruction of erythrocytes by the malarial organisms. At the same time there may be extensive foci of induration and of destruction of the hepatic parenchyma (cirrhose paludéenne). In these cases there is usually an additional brownish, iron-containing pigment within the liver cells. [In hemochromatosis, with or without diabetes, there is marked brownish pigmentation of the extensively cirrhotic liver. Most of the pigment gives the iron reaction. See Opie, "Journ. of Exp. Med.," 1900, IV, 279-306; also Maude E. Abbott, "Journ. of Path. and Bact.," 1900, VI, 315-326.]

Finally, peripatetic processes with diffuse fibrous thickening of the capsule of the liver, often part and parcel of a chronic peritonitis, are usually accompanied after some time by cirrhotic indurations of the hepatic parenchyma [capsular cirrhosis].

LEUKEMIA.

In acute and chronic leukemia, as well as in pseudoleukemia, the liver partakes in a characteristic manner in the general process. In the earlier stages only the portal capillaries are filled with linearly arranged lymphocytes [and leukocytes] that stand out sharply from the liver cells on account of their deeply stained nuclei. Before long, the cells form denser aggregations, and even circumscribed, tumor-like masses, the so-called lymphomas. The seat of election is the periportal connective tissue, which soon becomes wholly infiltrated at certain points with thickly crowded cells. Later the groups of cells become connected by means of cellular prolongations, which may separate

PLATE 72.

FIG. 1.—Luetic Cirrhosis of the Liver with Cicatricial Retraction of the Capsule. $\times 35$. 1, The capsule of the liver; 2, cicatricial retraction of the capsule over a shrunken area almost wholly replaced by connective tissue; 3, large fibrous area with numerous biliary canals; 4, larger and smaller parenchymatous islands surrounded by connective tissue.

FIG. 2.—Diffuse Induration and Formation of Gumma in Congenital Syphilis in the Newborn. $\times 63$. 1, Newly formed fibrous tissue which has destroyed the lobular structure and crowded the cords of liver cells apart into smaller groups; 2, accumulation of round cells with beginning nuclear disintegration in the center and fibrous periphery (early gumma).

the acini from one another with unusual distinctness. Finally the infiltration extends concentrically inward between the liver cells toward the venæ centrales, leading in the most advanced instances to replacement of the liver cells by pressure atrophy. The increase in lymphocytes [and other cells] takes place not only by increasing deposition from the blood, but also by mitotic proliferation of the cells already present. Rounded, nodular accumulations of lymphocytes also occur within the acini. In the lymphomas there is always a fine network of delicate connective-tissue fibers, in the meshes of which the cells are suspended. The atrophic liver cells often contain ferruginous pigment derived from the great destruction of red corpuscles.

Quite similar infiltrations in the liver, only often much larger, occur in pseudoleukemia.

INFECTIOUS GRANULOMAS.**(A) TUBERCULOSIS.**

Tuberculosis of the liver occurs in two principal forms: as circumscribed, apparently irregularly disseminated nodules, which by further growth coalesce to form larger nodes; and, secondly, in close connection with the biliary ducts.

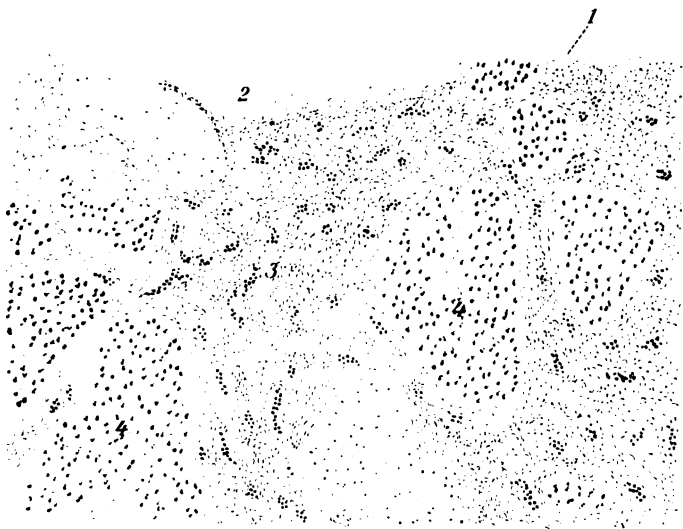


Fig. I.

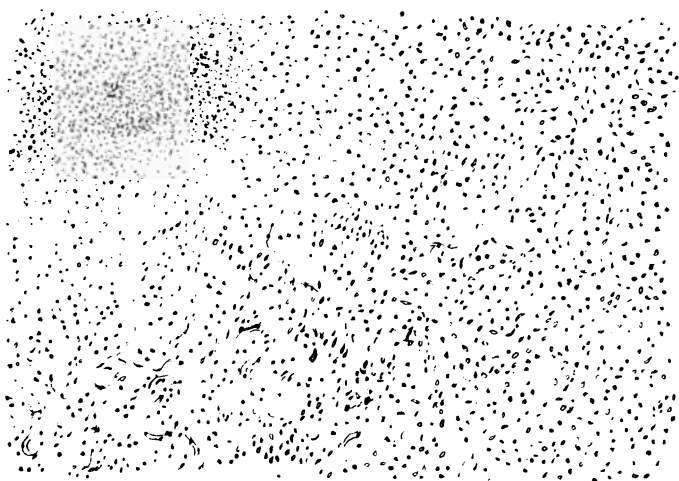


Fig. II.

The first form, disseminated tuberculosis of the liver, is exceedingly common. Macroscopically the earlier stages are often overlooked, but a fairly thorough microscopic study of the liver hardly ever fails to disclose the presence of tubercles in cases of chronic or acute tuberculosis elsewhere. (Simon found them in eighty-two per cent. of the cases examined; in ninety-five per cent. among children.) In tuberculosis of the intestines, which is so common, micro-organisms are carried to the liver in the portal blood.

Liver tubercles are often exceedingly small, and in recent cases the organ offers the best opportunity to study the histology of acute tubercle, as well as of its further growth. The young nodules are found oftenest in the immediate vicinity of the periportal connective tissue and extending into the outskirts of the lobules. They are built up at first by a few epithelial cells, which are derived from the fixed connective-tissue cells as well as from the liver cells by indirect division. The genesis of giant cells has been referred by Arnold especially to the epithelium of the biliary ducts. At a certain age the tubercles in the liver are rich in giant cells, which are mostly rounded or oval with smooth margins, the pseudopodial prolongations seen so commonly elsewhere being quite rare in the liver (Plate 70, Fig. 1).

The nodules become surrounded by a peripheral zone of round cells, and in the course of further growth they come together; hence the tubercles visible to the naked eye generally appear to be made up of several follicular formations. In the neighborhood there is often connective-tissue proliferation, which after a time may assume a cirrhotic character even to the extent of possessing the proliferations of bile ducts referred to in the foregoing.

Occasionally larger, nodular, tuberculous growths occur in the liver, especially in children. The microscopic examination, however, shows plainly in the margins confluence of single small tubercles.

The second form of hepatic tuberculosis is marked by the formation of larger foci, which tend to central disintegration, and which stand in a certain relation to the bile ducts. In these cases the liver is more or less thickly beset with greenish icteric nodules or cavities, often somewhat larger than a hazelnut. Microscopic examination shows that it concerns larger confluent tubercles, which are scattered in the immediate vicinity of the walls of the larger bile ducts or have ruptured into their lumens. The interior of the cavities is generally filled with caseous masses tinged with bile. The walls of the bile ducts may be traceable for some distance, and the cylindrical epithelium may be present at least in part. The peripheral portions of the nodes again show the development by fusion of smaller tubercles.

Formerly the opinion prevailed that this tuberculosis of the bile ducts (*cholangitis* or *angiocholitis tuberculosa*) originated from the entrance into the ducts of infectious material from the intestines. The virus was thought to penetrate the biliary epithelium without producing any lesions in it, and an eruption of miliary nodules would take place in the surrounding tissues (*tuberculous periangiocholitis*), which in their further growth might lead to a secondary rupture into the lumen of the ducts. Examination of serial sections, as first carried out by Chiari and Kotlar, shows that tuberculous disease of the bile ducts invariably extends from without inward; the nodules spring up in the periportal tissue and coalesce, eroding the walls of the ducts and breaking through into the lumen. In this way genuine tuberculous cavities may form in the liver which in their genesis are directly comparable to the pulmonary cavities that develop from peribronchial foci.

(B) SYPHILIS.

Syphilis occurs in two forms in the liver: namely, as a diffuse interstitial productive hepatitis, and as circumscribed, specific, granulomatous formations or gummous

hepatitis. Combinations and transitions of these two forms are frequently observed. Both forms may develop in the acquired syphilis of adults as well as in congenital syphilis, but it may be said, as a general rule, that in the acquired syphilis gummous productions predominate, while in the congenital variety diffuse induration is the more frequent form. The microscopic appearances may differ considerably in children and in adults, and separate statements are consequently necessary.

Interstitial, syphilitic hepatitis does not necessarily present either microscopic or macroscopic characteristics, as it may appear as a cirrhosis which more frequently resembles the hypertrophic than the atrophic type. The parenchyma of the liver is separated by proliferating connective tissue into larger or smaller areas, which may show remnants of a distinct lobular structure or only irregular parenchymatous groups within the new connective tissue (Plate 72, Fig. 1). As in other forms of cirrhosis, circumscribed hyperplasias of liver cells occur, with the production of a tubular structure, the single cells often containing many nuclei. Within the connective tissue there occur also epithelial cylinders and convoluted and proliferated bile ducts. In the later stages the connective tissue tends to marked irregular shrinking, which, together with parenchymatous hyperplasia in other parts, produces the irregular furrows and deformations into large lobes that so long have been held as characteristic of syphilitic cirrhosis. As will be seen in the following, these changes may also result in other ways.

In the adult, circumscribed granulomas (gummas) may be met with at any stage.

Recent gummous hepatitis (Plate 71, Fig. 1) is characterized in the adult by the production of multiple nodules, which are generally evenly distributed throughout the organ, and, like tubercles, they are situated mostly in or near the periportal connective tissue. The cellular elements of which they are made up are quite similar to

PLATE 73.

FIG. 1.—Proliferation of Glissonian Tissue in the Liver of the Newborn with Congenital Lues. $\times 75$. The periportal tissue is greatly increased and concentrically arranged. 1, Bile duct; 2, portal branch with thickened wall.

FIG. 2.—Diffuse Induration of the Liver in the Newborn with Congenital Syphilis. $\times 280$. 1, Greatly increased fibrous tissue between the columns of liver cells. Capillary epithelium proliferated; 2, cellular accumulation with beginning nuclear fragmentation (gumma).

those in tuberculosis: namely, round, epithelioid, and giant cells. In syphilitic granulomas, however, spindle cells are predominant, especially in the peripheral districts, and the demarcation from the healthy tissue is not nearly so marked as in tubercles, the cell infiltration passing gradually outward among the more or less disarranged cellular columns. In the center of the gumma there occurs a caseous necrosis, in which may be recognized for some time coarser, leaf-like structures (Plate 71, Fig. 1).

By confluence of adjacent nodules, gummous formations may reach a very considerable size, up to that of the closed hand. These large masses consist mostly of a wholly caseous, structureless material, in which may be found in later stages extensive calcareous incrustations, staining intensely blue with hematoxylin (Plate 71, Fig. 2). The peripheral spindle cells are changed into a dense fibrous capsule, in which may occur numerous vessels with greatly thickened walls and well-nigh occluded lumens (Vol. I, p. 42), smaller heaps of round cells, and scattered foci of liver cells.

When not calcified, considerable absorption may take place in the caseous centers of large gummas. Connective tissue passes in and produces circumscribed shrinkings that may correspond to funnel-shaped retractions of the surface. In this manner also may arise the irregular, coarse lobulation of the syphilitic liver.

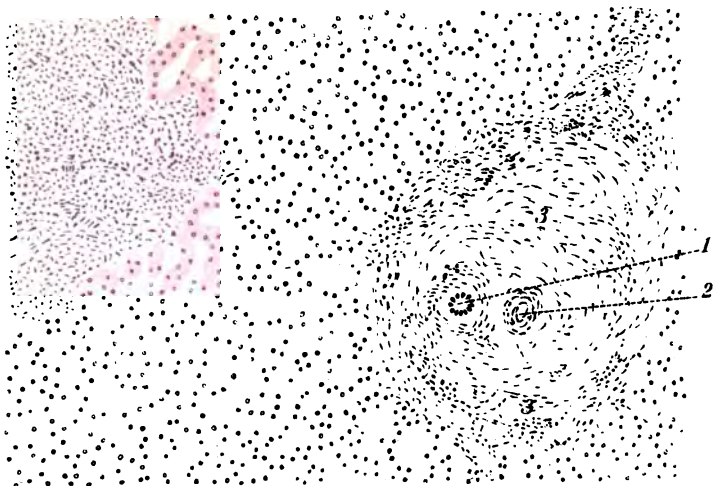


Fig. I.

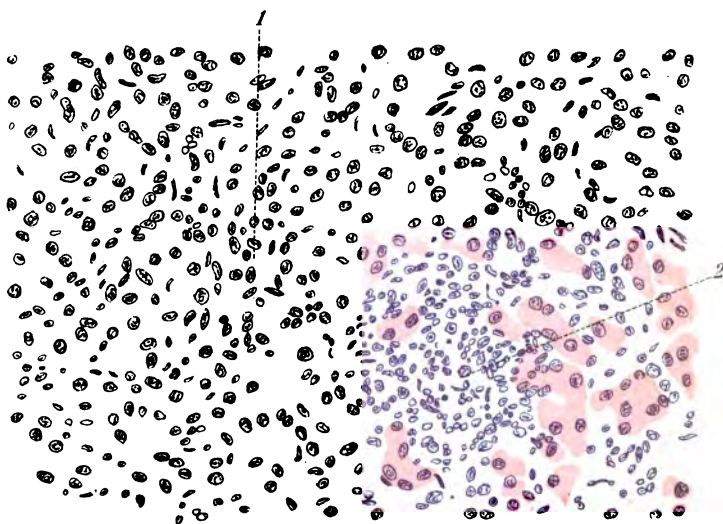


Fig. II.



The relatively frequent occurrence of congenital syphilis is probably explainable by the circumstance that the virus is brought directly to the liver by the umbilical vein.

In congenital syphilis of the liver diffuse induration is the most important change. The columns of liver cells are separated widely and completely disarranged as regards lobular order by broad bands of richly cellular connective tissue. This new tissue is very often densely arranged in concentric layers in certain places, especially around the portal branches and the bile ducts, and the blood-vessels may be wholly obliterated (Plate 72, Fig. 2). This proliferation and increase of the Glissonian tissue is often apparent at the hilus, whence it may be traced into the parenchyma.

Multiple miliary and submiliary gummas are not rare in the newborn. They are mostly interacinous nodules of epithelioid and round cells. Proliferated capillary epithelium probably takes part in the process; for there is at least considerable increase of epithelial cells between the trabeculæ of the lobules (Hutinel and Hudelo). The liver cells may contain two or more nuclei.

In all forms of syphilitic hepatitis, as well in adults as in children, there is often a considerable increase of elastic fibers, strands of which may pass into the lobules to the central vein.

ECHINOCOCCUS OF THE LIVER.

Of the parasites in the liver, the echinococcus especially is of histologic interest. This is the larval stage of the *Tænia echinococcus* of the dog (wolf and jackal). The eggs reach the human intestinal canal, the shells are dissolved, and the embryos are taken up by the portal radicles and carried to the liver, where they develop into vesicles. This will explain why the liver is by far the most frequent seat of echinococcus. Metastases may form in other organs, such as the glands at the hilus of the liver, the spleen, the lung, the heart etc.

PLATE 74.

FIG. 1.—**Alveolar Echinococcus of the Liver.** $\times 26$. (Picrocarmin.) 1, Remnants of liver tissue ; 2, connective tissue infiltrated with round cells ; 3, small echinococcus cysts lined with folded, chitinous membrane.

FIG. 2.—**Echinococcus Scolex from Alveolar Echinococcus of Liver.** The membrane of the cyst on the left. 1, Rostellum with hooklets ; 2, calcareous granules.

FIG. 3.—**Chitinous Membrane from Echinococcus cysticus of Liver.** $\times 385$. Note the longitudinal striation due to lamellated arrangement. To the right the more loosely arranged parenchymatous layer.

In man, as well as in the beef, sheep, and swine, two distinct forms of echinococcus are distinguished. *Echinococcus cysticus* and *Echinococcus alveolaris*.

1. **Echinococcus cysticus** (*hydatidosus*) is by far the more frequent. In the north of Germany it is the only form. [In the United States echinococcus is rare.] The vesicles may reach a size varying from that of a hazelnut to that of a man's head. The membrane is characteristic, and shows microscopically a lamellated structure of concentric homogeneous layers. It consists mostly of chitin. When boiled with sulphuric acid, grape-sugar appears. Especially in the older and larger vesicles, this membrane is surrounded externally by a thick capsule of connective tissue, which may send radiating prolongations into the surrounding tissue. It usually contains proliferated biliary ducts such as are seen in cirrhosis. When only one cyst is present (*Echinococcus unilocularis*), the heads of the parasites, or scolices (*scolex*), are situated directly upon the inner and more loosely arranged layer of the cuticle. A scolex presents a small conical process (the *rostellum*), four oval suckers, a circle of glistening and stiletto-like hooklets, and usually numerous round and oval calcareous concretions. The entire scolex is usually invaginated into the shorter, posterior, pedunculated part, the so-called cer-

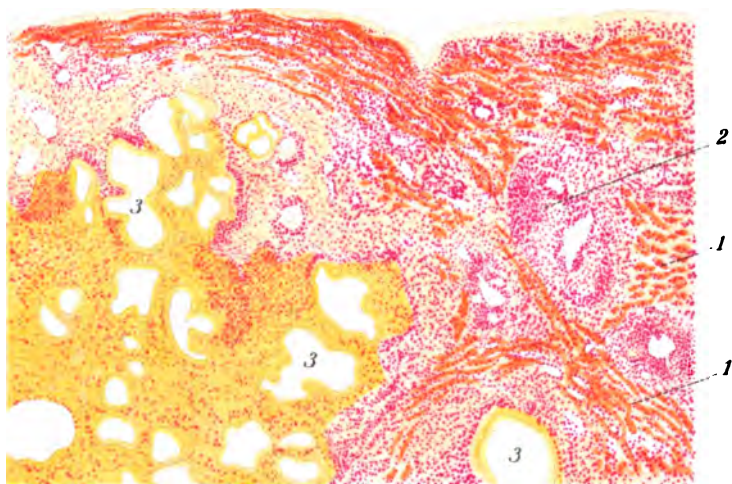


Fig. 1.



Fig. 2.

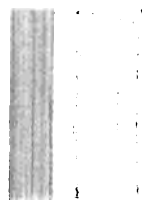
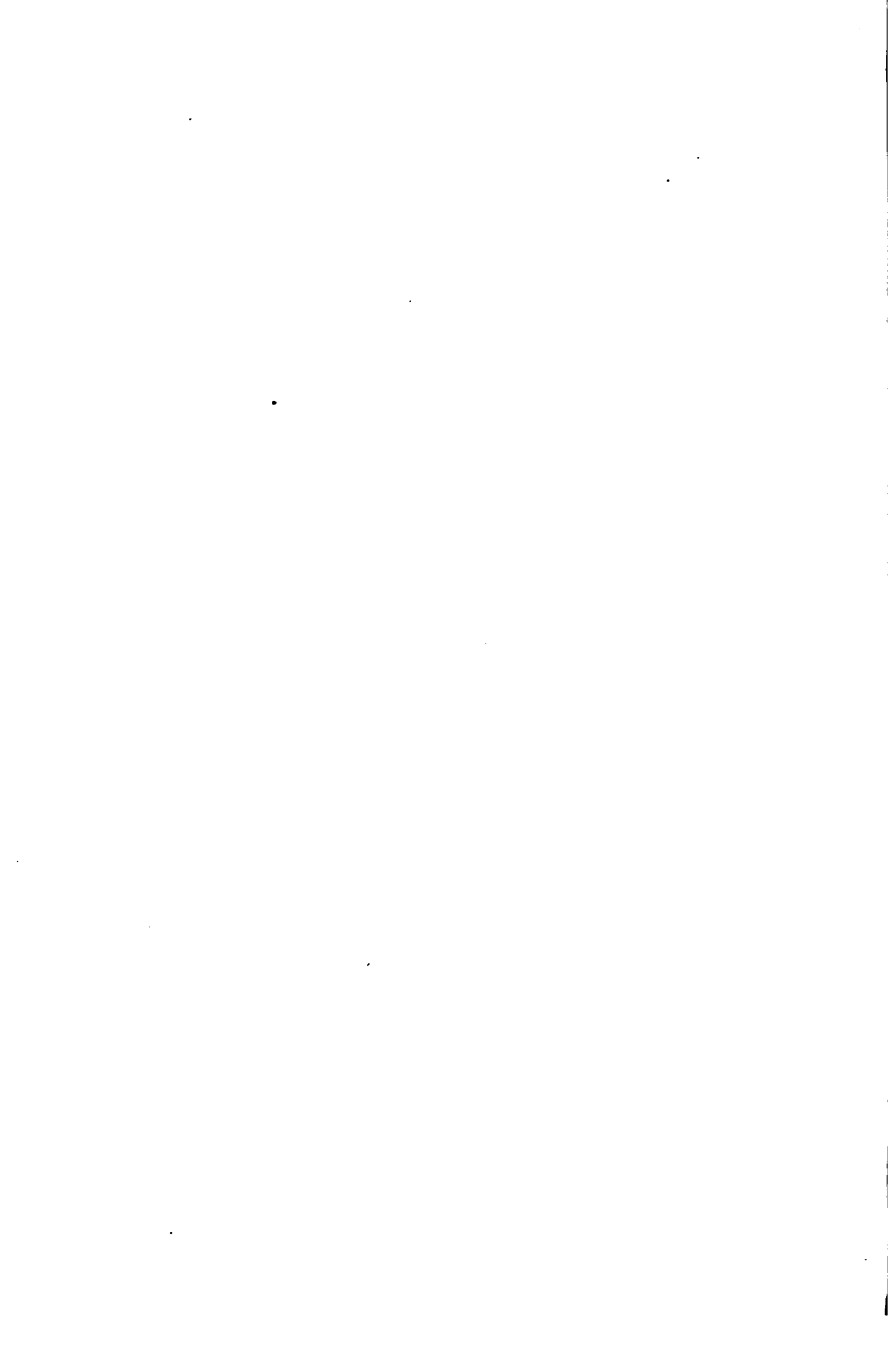


Fig. 3.



vical portion. The form in which the scolices are situated directly upon the inner surface of the primary cyst, forming small granules, is known as *Echinococcus granulosus*. Often, however, the principal cyst may contain daughter cysts (up to fifty or more), and this again granddaughter cysts, which may contain scolices or be sterile. In addition, the snaring off of daughter cysts externally gives rise to the so-called *Echinococcus exogenus*.

Dead echinococcus cysts are frequently found in cadavers. The diagnosis is then made certain only by finding the typically lamellated chitinous membrane or pieces thereof, or scolices and hooklets. In addition, there are usually found calcareous concretions, and at times the whole cyst has been changed into a chalky or mortar-like mass, so that the calcareous materials must be dissolved out with hydrochloric acid before the characteristic elements are made demonstrable, mixed with fat, cholesterin, and granular cells. Suppurative and septic processes may develop in echinococcus cysts, due to the entrance of intestinal micro-organisms. In this way may be simulated primary abscesses of the liver the real nature of which is made clear only by microscopic demonstration of the membrane or hooklets.

In the presence of large vesicles the remaining liver tissue often shows a distinct compensatory hypertrophy with enlargement of the lobules, the cellular trabeculæ, and the liver cells, the latter containing numerous karyokinetic figures (Ponfick).

2. The second form of echinococcus, *Echinococcus alveolaris* (also called *multilocularis*), occurs especially in south Germany, Tyrol, Switzerland, and southeastern Russia. It forms larger growths in the liver, of a distinctly alveolated, spongy structure. Its parasitic nature was first recognized by Virchow, it having been diagnosed previously as alveolar colloid carcinoma. The cysts are composed of innumerable very minute vesicles, lined with a greatly folded and wrinkled membrane, which has

the same structure as in *Echinococcus cysticus*. The small cavities may contain scolices; but more commonly they are sterile, containing sometimes a granular material consisting of fat, cholesterin, calcareous particles, and biliary pigment masses. In the early stages the development of the vesicles may be traced in the lymph-vessels of the liver (Virchow), but later they get into relation with the blood-vessels and larger bile ducts.

A marked connective-tissue proliferation usually takes place around the vesicles, so that only remnants of compressed and atrophic liver parenchyma are seen (Plate 74, Fig. 1). This connective tissue contains also proliferated bile ducts, round-cell accumulations, and often also giant cells. Calcareous particles, blood pigment, and biliary pigment may be deposited in this tissue. By softening of the membranes numerous alveoli may coalesce to form larger cavities, which appear to be filled with a puruloid material. Real suppuration from the entrance of bacteria also occurs. [For a recent extensive study of *Echinococcus alveolaris*, see Melnikow-Raswedenkow, iv. Supplementheft of Ziegler's Beiträge, 1901.]

THE PANCREAS.

The histologic structure of the pancreas resembles in general that of the salivary glands, especially the parotid. The structure is consequently that of a tubulo-acinous gland. The ducts are lined with a single layer of cylindrical epithelium. They are continued into the gland as short tubes, lined with low cells, and extend for some distance into the alveoli as intralobular ducts, the cells of which are known as centro-acinar cells. The cells of the glandular acini are large, more or less pyramidal in shape, and present two zones in the fresh, secreting organ. The inner zone, nearer the glandular duct, is darker, coarsely granular, and filled with particles of the so-called zymogen which is assumed to be the mother of the specific ferment of the gland, trypsin. The particles swell up in water and are eventually dissolved by it. The broader, external zone of the gland cells is clear, almost wholly homogeneous. In it is located the round, vesicular nucleus; and often there are two nuclei in one cell. Secretory

capillaries pass between the cells as far as the zymogenic zone and empty into the lumen of the ducts.

At certain points in the interior of the lobules, or between them, are larger rounded or oval heaps composed of large, clear, and homogeneous cells. These masses are known as "the bodies of Langerhans," after their discoverer. They are separated by connective tissue from the surrounding secreting tissue and do not possess any ducts. They contain very large capillaries, and as the cells are situated directly upon the capillary walls, they have been regarded as glands with an internal secretion, like the hypophysis.

Of the pathologic processes in the pancreas necrosis, though known for but a short time, is the most important. As it is closely related to the so-called fat-necrosis, this is also considered at this time.

Small scattered islands of necrosis are very common in the pancreas. As shown by Chiari, they must be regarded as the result of autodigestion caused by diffusion of the digestive pancreatic ferment, trypsin, and they may occur either after death or during life. In the first case the microscopic examination reveals that smaller or larger areas of the glandular lobules have been changed into homogeneous necrotic masses, in which the nuclei are not stained and in the vicinity of which there are no evidences of reactive changes. In the intravital necroses the necrotic area is surrounded and separated from the adjacent tissue by a zone of inflammatory tissue infiltrated with leukocytes (as in the case of infarcts). In the early stages the borders of the cells disappear and the cells of the affected alveoli run together into multinuclear heaps (Plate 75, Fig. 1) which show a progressive vacuolization, and eventually the nuclei disappear wholly. Langerhans' bodies persist the longest. Local anemia, caused by contraction of the arteries and by endarteritic processes in the pancreas, has been made responsible for this necrosis (Beneke, Blume, Chiari). Under certain conditions the necroses may become very extensive; large parts of the pancreas may be exfoliated, and the erosion of vessels not infrequently has led to fatal hemorrhages ("pancreatic apoplexy"). [Important contributions to the study of

PLATE 75.

FIG. 1.—Fatty Degeneration [?] and Necrosis of Pancreas.

× 74. 1, Parenchymatous zone in which the cells have coalesced into larger cell groups; 2, broad connective tissue bands with necrotic nuclei; 3, necrotic fat tissue with "latticed" structure.

FIG. 2.—Necrosis of Pancreas. Fresh teased preparation. × 280.

There are numerous larger and smaller fat globules. Some have a semilunar, hyaline zone (to the left and below). There are bundles and radiating masses of crystalline fatty acids.

pancreatitis, experimental and otherwise, have been made recently by Flexner and Opie. Their articles may be found in "Contributions to the Science of Medicine by the Pupils of Wm. H. Welch," 1900, "The Bulletin of the Johns Hopkins Hospital," and in "Journal of Experimental Medicine."]

An almost constant concomitant condition of pancreatic necrosis is necrosis of the fat in the pancreas, as well as in the peripancreatic fat tissue, and, further, of the fat of the omentum and the mesentery; more rarely in the subserous abdominal fat, but occasionally even in the fat of the anterior abdominal wall and in the subpleural fat [and even in the fat of bone marrow]. The necrotic foci appear macroscopically as sharply circumscribed, yellowish-white, opaque areas, and they show marked microscopic alterations. The capsules of the large fat cells in fresh preparations are found to contain innumerable fat droplets, and often the nuclei appear increased in number. More commonly the fat shows signs of a still further advanced disintegrative process, as the rounded spaces are filled with radiating bundles of glistening crystalline needles (Plate 75, Fig. 2). It concerns the formation of salts by calcium and fatty acids (palmitic and stearic), as demonstrated by the appearance of typical rhombic crystals of gypsum by subjecting proper specimens to the prolonged action of pure sulphuric acid. About the bundles of crystals are often found homogeneous opaque masses.

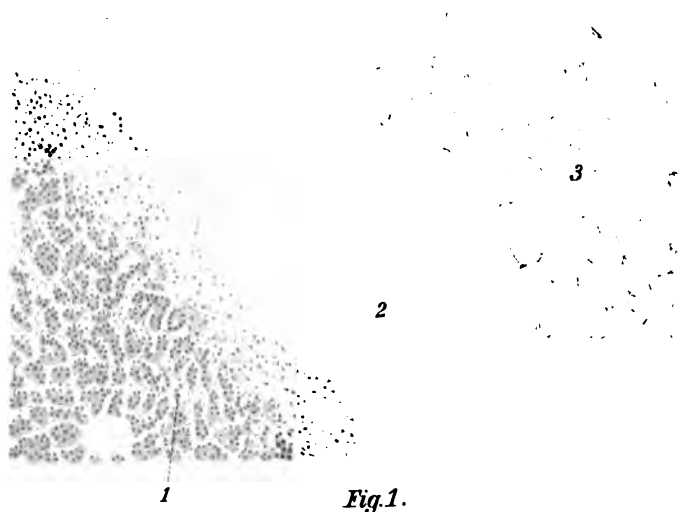


Fig. 1.

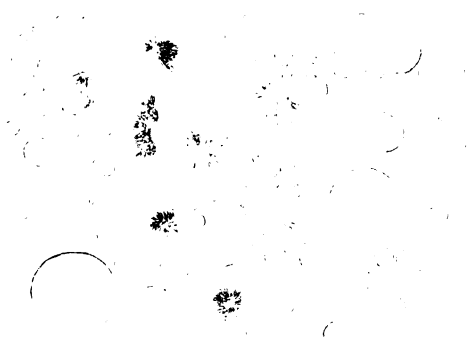


Fig. 2.

The persisting fat cells often show an annular or half-moon-shaped, hyaline, transparent outer zone, which is stained intensely blue with hematoxylin (Plate 75, Fig. 2). Sections of hardened preparations of the necrotic fat tissue show a peculiar lattice-like ("fachwerkähnlicher") structure (Katz and Winkler).

There is good reason to believe that this characteristic change in fat stands in causal connection with primary disease of the pancreas, the course of events being traceable to the liberation by the retrogressive changes in the gland of the fat-splitting ferment of the pancreas (steapsin). This view is strengthened by the recent observations (M. B. Schmidt) of multiple intra-abdominal fat-necrosis following traumatic ruptures of the pancreas. [Flexner found steapsin present in necrotic foci at certain stages of the process. The subject has also been investigated by Herbert U. Williams and by Opie.]

Of other processes of histologic importance in the pancreas may be mentioned infectious granulomas both tuberculous and syphilitic. The first appears in the form of circumscribed nodules of characteristic structure, most commonly interacinous, and usually as a terminal dissemination in cases of chronic pulmonary tuberculosis as well as in typical general miliary tuberculosis.

Syphilis of the pancreas is observed especially in the congenital infection of the newborn, and mostly as a diffuse, often highly cicatricial induration of the gland, the specific gland cells being crowded out by a dense fibrous tissue. The lobules may disappear except for a few groups and bands of epithelial cells. (Langerhans' bodies seem to persist uninjured.) Genuine gummas are more rare, but they occur occasionally as well in the newborn as in the tertiary stage of acquired syphilis. They show central caseous necrosis and peripheral fibrous encapsulation.

Pigmentation of the cells of the pancreas occurs as part of general pigmentary deposition, as in alcoholics with v. Recklinghausen's pigmentation of the intestinal muscu-

laris (Vol. I), in senile persons with general atrophy of the organs (brown atrophy) [and in hemachromatosis with or without diabetes, the pancreas being cirrhotic].

[There are two principal forms of cirrhosis of the pancreas, the interlobular and the interacinar; in the former the islands of Langerhans remain intact except in advanced cases. Opie (Jour. Exp. Med., 1901, v, 397-428) shows a relationship between lesions of islands of Langerhans and diabetes mellitus.]

THE URINARY ORGANS.

I. THE KIDNEYS.

The kidney is a compound tubular gland. The single tubules are called uriniferous. They are partly convoluted, partly straight. The first are found in the cortical substance only, the last principally in the medullary substance, the striation normally seen in it being due to the straight course of the tubules. The uriniferous tubules arise in the cortex in an ampulla into which an arterial [capillary] plexus is pushed in a peculiar way—the Malpighian body. The vascular bunch or glomerulus, which enters the ampulla, is covered with a continuous layer of flat epithelial cells with somewhat prominent nuclei. Von Ebner (in Koelliker's "Handbuch der Gewebelehre des Menschen," VI. Aufl., Bd. 3) regards the epithelial layer as an unbroken syncytium, which, as a whole, covers the capillary loops of the glomerulus.

The epithelial covering passes over upon the inner surface of the capsule that surrounds the glomerulus—Bowman's capsule. Normally a free space exists between the capillary loops and Bowman's capsule from which the urinary tubule departs. Its beginning is convoluted—*tubulus contortus* of the first order [proximal convoluted portion]—and located in the so-called labyrinth of the cortex. In the peripheral parts it passes first to the most external part of the cortex,—Hyrtl's cortex corticis,—in which there are no glomeruli, whence it turns back into the cortex and forms Henle's loop, composed of two parallel limbs [descending and ascending] and often extending into the medullary substance. The descending limb is narrow and thin-walled, the ascending being thicker. They do not run in the labyrinth of the cortical substance, but form a part of the medullary rays or Verheyen's pyramids, between which run the convoluted tubules in the cortical labyrinths. The ascending limb of Henle's loop ends in a convoluted portion, which passes from the medullary ray into the cortical labyrinth—*tubulus contortus* of the second order [distal convoluted portion]—and ends in a straight tubule—*tubulus rectus*—that passes directly into the medullary part. By the coalescence of several tubuli

recti arise collecting tubules, which in turn form the ductus papillares, the diameter of which varies up to 0.3 millimeter, and which, to the number of twenty to twenty-five, empty at the "cribrum bendictum" [foramina papillaria], in the apex of the papilla. The human kidney consists of ten to twelve divisions into Malpighian pyramids, each ending in a papilla.

The uriniferous tubules consist of a homogeneous structureless basement membrane, or *membrana propria*, upon which are situated the epithelial cells, which differ in structure in various parts of the tubules. The cells are lowest, almost fully flat, and polygonal in the Malpighian bodies, on the surface of the capillary loops as well as upon the inner layer of Bowman's capsule. In the neck of the convoluted tubules of the first order it becomes cylindrical, the borders of the individual cells being indistinct. The basal portion of the cells—that is, the part near the basement membrane—shows a fine longitudinal striation as far as the nucleus, while the part near the lumen carries a layer of extraordinarily fine cilia. ["In well-fixed preparations the inner portions of the cells show a narrow, striated border, often giving the appearance of short cilia."—Böhm, Davidoff, and Huber.] The basal striation is the result of the arrangement of the protoplasmic granules into regular rows; in the central parts the granules become somewhat larger and irregular, and small droplets of fat occur here normally. The cells in the descending loop of Henle are very low; the nuclei project somewhat and the alternating nuclear projections give the lumen a serrated appearance on longitudinal section. At the lower end of the loop the epithelium again assumes a taller, cylindrical form. The convoluted tubule of the second order and the straight tubules have cylindrical cells. In the papillary ducts the cells are especially tall and palisade, and less granular than in the convoluted tubules.

At the hilus the renal artery divides into several branches, which pass as *arteriæ interlobares* between the papillæ in the columns of Bertini to the border of the cortex and medulla, where they turn almost at right angles and continue as *arteriæ arcuatæ* or *arteriæ arciformes*, which send smaller branches (*arteriæ interlobulares*) [intralobular arteries—Böhm, Davidoff, and Huber] into the cortex between the medullary rays. From the *arteriæ interlobulares* arise smaller twigs, each passing as the *vas afferens* to a glomerulus. Within the glomerulus the *vas afferens* forms a varying number of loops, and emerges as the *vas efferens*.

(Von Ebner assumes that the glomerular capillaries are devoid of epithelial lining; that they are homogeneous membranes covered by the syncytial layer mentioned before.)

Beyond the glomerulus the *vas efferens* forms a capillary network which surrounds the uriniferous tubules, whence the blood is carried by *venæ interlobulares* [intralobular veins—Böhm, Davidoff, and Huber] into *venæ arcuatæ*, which empty in *venæ interlobares*. Some of the peripheral glomeruli are supplied by arterial twigs from the renal capsule (*arteriæ capsulares glomeruliferæ*). The capillaries in the cortical labyrinth empty their blood into the *venæ stellatæ Verheyinii*, from the centers of which interlobular veins arise.

II. THE EXCRETORY URINARY PASSAGES.

The excretory urinary passages consist of three layers—fibrous, muscular, and mucous. The first consists of fibrous tissue and elastic elements. The ureters possess an external transverse and an inner longitudinal layer of smooth muscle-fibers, which are continued into the renal pelvis.

The mucosa has a vascular stratum proprium and a many-layered epithelium, the upper strata of which consist of large and flat cells and give a serrated or festooned appearance when seen in profile from below. Then follow cylindrical and club-shaped cells, while the lower layer consists of small round epithelial cells. Leukocytes are often seen passing through between the cells. In some places the epithelium sinks down and forms depressions, but glands and papillæ are not found in the pelvis, the ureters, and the bladder. The epithelium rests upon a homogeneous basement membrane. Dense accumulations of lymphocytes occur under the epithelium, often in follicular form. There is no real submucosa, but the stratum proprium passes into the muscularis with sharp borders. The urinary bladder has a triple layer of muscle-fibers—an outer longitudinal layer, and under this a network of oblique and transverse fibers. The crypt-like depressions of the epithelium in the urinary passages occasionally give rise to cysts (Lubarsch).

Circulatory Disturbances.

Passive hyperemia of the kidneys is found frequently at postmortems, especially in cases of hypertrophy of the heart, as seen particularly in beer-drinkers [this book is written in Munich], in fatty heart, in valvular disease of the left heart in consequence of chronic endocarditis of the aortic or mitral valves; furthermore in many pulmonary diseases (emphysema, chronic pulmonary tuberculosis), and sometimes also from local circulatory disturbance on account of thrombosis of the inferior vena cava. In the earlier stages of passive congestion the kidneys are large, deep brownish-red, the surfaces smooth. This condition is constantly found after death from asphyxia. Microscopically there is marked hyperemia of the venous channels, extending into the capillaries and the glomerular vessels (Plate 76, Fig. 1). The capillaries are filled with red blood cells, and on this account the distance between the transverse sections of the uriniferous tubules appears widened. Occasional corpuscles are found

in the lumen of Bowman's capsule and of the tubules (Plate 76, Fig. 1).

Longer continuation of the congestion is sure to cause increase in consistence of the kidneys, as in other organs subjected to increased blood pressure (compare "Passive Congestion of the Lungs," Vol. I, p. 83). As the venous hyperemia gives the organ a bluish-red color, the condition is called cyanotic induration. With time, the surface becomes granular and the kidneys undergo a progressive diminution, which may end in a genuine granular atrophy (granular congested kidney).

The histologic changes now become quite complicated. Radiate sections show many foci in the cortex, with a high grade of ectasia and congestion of the venous (and arterial) vessels and capillaries, around which are cell accumulations (Plate 76, Fig. 2). If the surface is uneven, then the cellular foci will be found to correspond to retractions, while the "granula" [or projections] are formed by apparently normal tissue.

Closer examination of the foci of infiltration reveals that the uriniferous tubules in them are often diminished in size, the transverse sections and the lumens narrow, the epithelium lifted from the basement membrane and dislocated into the lumen.

In many tubules there is thickening of the basement membrane, which appears glistening, homogeneous, and swollen; and the capillary walls also appear somewhat thickened and homogeneous, the nuclei of the lining cells are increased in number, and the exterior covered with long, spindle-shaped cells. The spaces between the tubules and capillaries seem wider on account of this increase in the ground substance, which often may be finely fibrillated or granular, inseparably amalgamated with the thickened basement membranes, the latter appearing to contribute to the increase in the interstitial tissue. Occasionally the thickened basement membranes form empty and collapsed rings in which the epithelium has been desquamated and

PLATE 76.

FIG. 1.—Passive Congestion of Kidney. $\times 130$. All capillaries and veins, as well as the loops of the glomeruli, are highly ectactic and filled to distention with red blood-cells. The urinary tubules contain vacuolated albuminous masses, and in the capsular space of the glomeruli is coagulated albumin.

FIG. 2.—Cyanotic Induration of the Kidney. $\times 54$. All blood-vessels are dilated. 1, Subcortical [subcapsular] cortical zone; 2, indurated focus in which the interstitial tissue is increased and cellular, Bowman's capsules thickened, and the uriniferous tubules compressed, in part absent.

lost. Occasionally the epithelial cells have coalesced into one mass within such spaces. Large accumulations of round cells are comparatively rare in the widened interstitial bands.

The foci of this character are found always in the immediate vicinity of dilated and congested veins, and especially where the superficial stellate plexuses unite to form venæ interlobulares. It is here that the earliest cicatricial retractions appear. The adventitia of the veins is considerably thickened and contains numerous collagenous and elastic fibers, which pass out into the surrounding connective tissue. The walls of the arteries within these foci are found often much thickened, the increase occurring in the adventitia and in the intima as well as even in the muscular coat. The thickening and cell proliferation usually extend to the smaller vessels, more particularly the vasa afferentia and efferentia of the glomeruli.

The Malpighian bodies in the early stages of cyanotic induration show a marked injection of the capillary loops, occasional red blood cells escaping into the capsular space. Later the capsular spaces generally contain an annular or semilunar-shaped zone of transuded albumin, which is made very distinct by placing the pieces in boiling water for a short time or in concentrated sublimate solution, which coagulates the albumin (Plate 76, Fig. 1). The

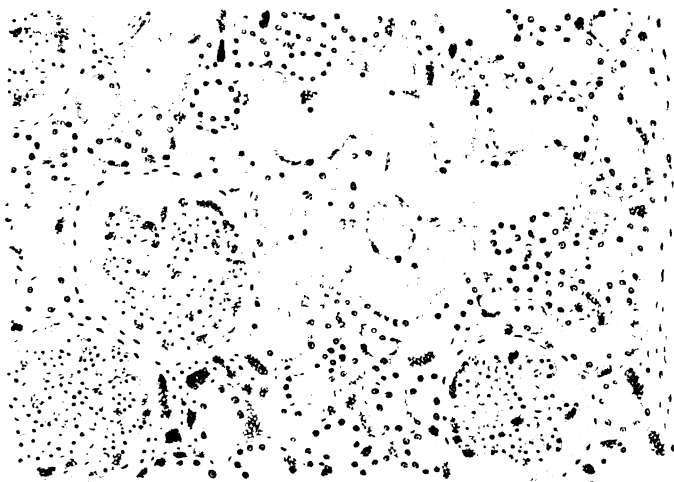


Fig. 1.

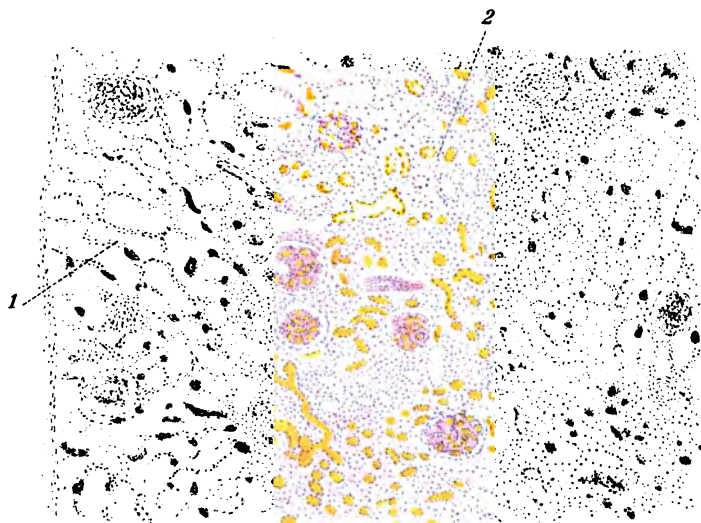


Fig. 2.



epithelium of Bowman's capsule as well as of the capillary loops shows swelling, cloudiness, nuclear proliferation, and desquamation, so that larger epithelial masses are often found in the capsular space which later may undergo fatty changes. These are changes that are met with again in all inflammatory processes of the kidneys.

Later there is established progressive increase in the thickness of Bowman's capsules, which begins in the same manner as described in connection with the basement membrane of the uriniferous tubules. Gradually single capillary loops become occluded and assume a homogeneous, "hyaline" appearance without giving any special staining reactions. At this stage there may be quite marked cellular accumulations about the vascular peduncles of the glomeruli, and the impression is obtained that this compresses the vessels. As little by little the glomerulus melts together, as it were, with its capsule, the capsular space is obliterated, beginning at the hilus and gradually spreading to the capillary loops. The increasing thickness of the capsule, the formation of a concentrically fibrillated connective tissue with but few nuclei, and the occlusion of capillary loops eventually transform the whole Malpighian body into an acellular and anuclear homogeneous, glistening ball—a process that develops in the same manner in chronic inflammatory conditions.

The medulla is also affected. The uriniferous tubules appear separated by a homogeneous or fibrillar material with but little cell infiltration. The arteriæ arcuatæ show a broader adventitia, from which fibrous prolongations radiate into the surrounding tissue. The medullary rays are relatively least involved in the interstitial increase.

In long-continued but slowly advancing instances extensive shrinking takes place in the interstitial tissue, and thus arises a typical granular atrophy, which is distinguished from genuine contracted kidney only by the persistent hyperemia and by the fact that the genesis may still be traced by the increased thickness of the vascular

walls. Secondary and extensive fatty changes often take place in the tubular epithelium, and hyaline and granular casts are found.

Infarcts.

As the arteries of the kidney are terminal arteries in Cohnheim's sense (*i. e.*, arteries that do not communicate with one another by means of anastomoses), it follows that the embolic (or thrombotic) occlusion of an arterial branch is followed always by the formation of an area of anemic necrosis. The size of the infarct varies according to the size and importance of the occluded vessel; the shape is always that of a wedge, the point directed toward the hilus [those involving the cortex only are more quadrilateral]. The point usually lies in the medulla, while the base generally reaches to the surface or is separated from it by a thin layer of healthy tissue when the blood supplied by the capsular arteries suffices to maintain the nourishment.

Microscopically the recent infarct is sharply differentiated from the surrounding tissue by the changes incident to necrosis (Plate 77, Fig. 1). Even the unstained section shows clearly the blurred, opaque, grayish appearance of the parenchyma. While the nuclei of the adjacent cells are rendered distinct by the addition of acetic acid, this agent has no such effect upon those of the infarct. But at the margins there is some accumulation of nuclei and a circle of thickly distributed fat globules in the epithelial cells. Stained sections show complete absence of nuclei in the affected area. The general structure of the tissue is retained, for the uriniferous tubules and glomeruli are recognizable, but the nuclei are absent and cannot be made visible by any of the usual stains. Evidently the chromatin is lost, and as the examination of fresh tissues with acetic acid demonstrates that the achromatic nuclear substance also is absent, it follows that a real and complete disappearance of the nuclei has taken place. The distinctions in structure and staining properties between nucleus

and cell body are destroyed. The cell bodies proper also are changed: the borders between the individual cells have disappeared. The lumens are ringed by material which retains color poorly even when treated with diffuse stains, and is provided with irregular serrations upon the inner surface. Small fat droplets are often present. Sometimes desquamation has taken place and irregular flakes lie in the lumen. The cilia and the longitudinal striations are wholly lost, and, except for the vacuoles, the necrotic epithelial cells have no structure whatever. After a longer time the nuclei of the interstitial tissue also lose their affinity for stains, retaining their vitality better than the tubular epithelium. Hence in the earlier stages the nuclei of the intertubular capillaries may be demonstrable, while the tubular epithelium has lost its nuclei completely.

The loss of nuclei and the increasing disintegration of the cells is the result of a coagulation of the cells of the necrotic area, produced by an infiltration of plasmatic fluid from the surrounding healthy tissue (Weigert). The lymph permeates the necrotic areas and dissolves the chromatin, hence the disappearance of the nuclei [karyolysis]. As the cells perish fibrinogen is set free, and actual fibrin may be formed. The fibrin stain then shows a fine network of fibrinous threads in the capillaries between the tubules, and sometimes in the tubules, and especially at the margins of the infarct.

After a time the picture changes materially. At the margins thick accumulations of nuclei take place, and even with low power they form a dark circle. Closer study shows that the nuclei are arranged in dense masses between the tubules, only a few being found within them or within the glomeruli (Plate 77, Fig. 2). It concerns leukocytes which have wandered into the infarct in response to the chemotactic influence of the necrotic tissue. They rarely reach the center, but accumulate mostly in the periphery. This leukocytic infiltration is only transitory. Before long the immigrated cells show fatty changes in the

PLATE 77.

FIG. 1.—**Anemic Infarct of the Kidney.** $\times 72$. 1, Wholly necrotic anuclear renal tissue; 2, marginal zone infiltrated along the interstitial tissue by leukocytes with fragmented nuclei.

FIG. 2.—**Margin of Anemic Renal Infarct** (giving detail of Fig. 1). $\times 260$. 1, Necrotic uriniferous tubules without nuclei, parts filled with loosened epithelium. In the center a necrotic glomerulus with anuclear capillary loops. In the interstices, and also in glomerulus, heaps of leukocytes with fragmented nuclei.

cell bodies and a peculiar disintegration of the nuclei. After a preliminary condensation of the nuclear membrane the nuclei are reduced to innumerable smaller and smaller fragments, which retain the nuclear stains to the last. This change, designated as karyorrhexis by Klebs, sometimes takes place in the nuclei of the uriniferous tubules and the glomeruli before the complete disappearance of the nuclei just described. Fresh preparations of this stage show the dark zone, produced by the leukocytes and the inclosed fat droplets, sharply distinguished from the healthy tissue on one side and the necrotic on the other; and stained sections are chiefly remarkable for the innumerable nuclear fragments, varying in size from a leukocytic nucleus to the minutest speck, and lying between the tubules (Plate 77, Fig. 2).

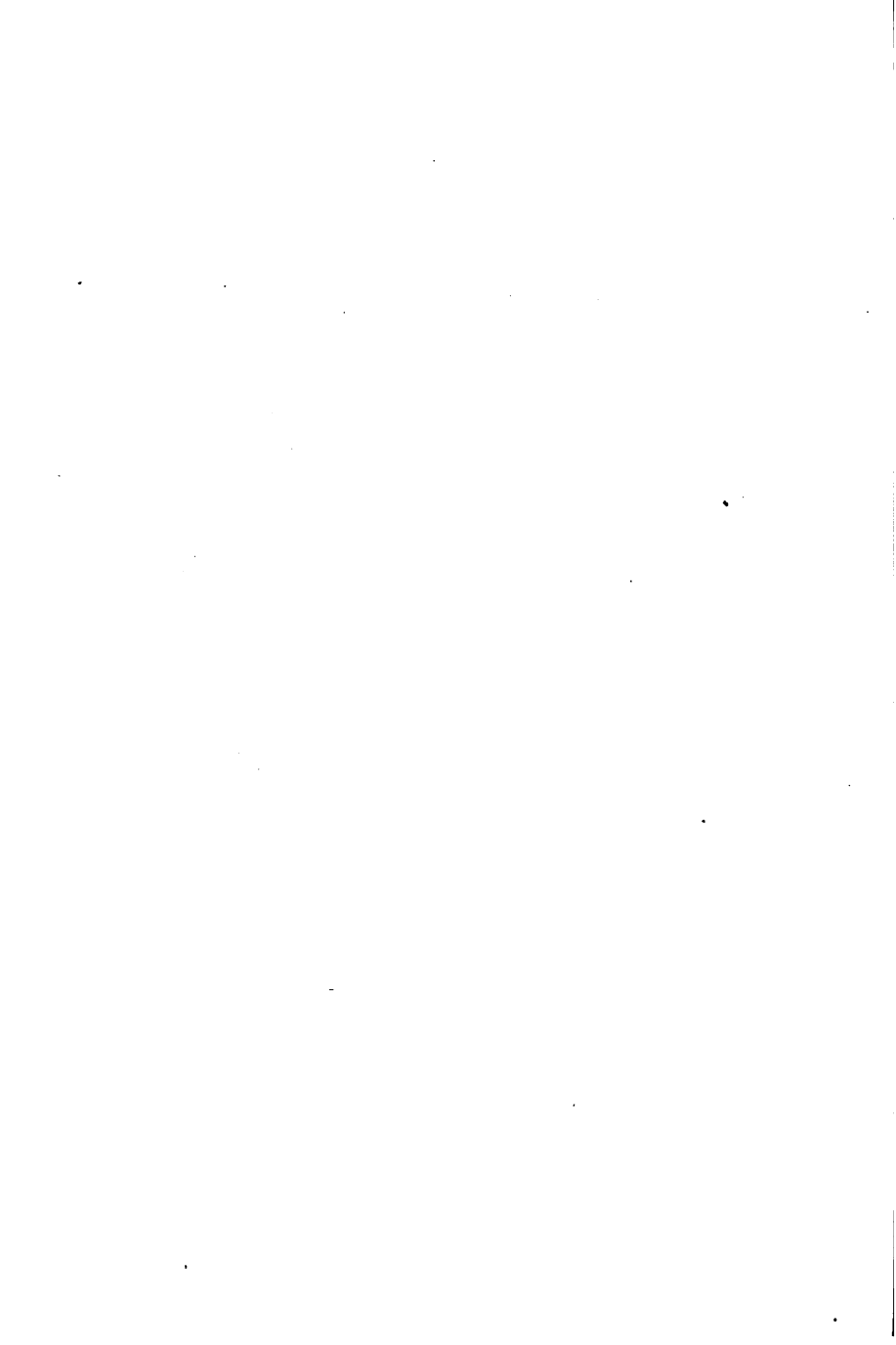
The blood-vessels in the neighborhood of the infarct—arterial, venous, and capillary—are usually dilated to the utmost. Occasionally the embolus may be found in a section of the afferent artery. The marked injection is caused by obstruction of the blood on account of the occluded vessels in the infarct. First there develops stasis in the capillaries and veins, shown by the accumulation of leukocytes along the walls, and later there may be a backward movement of the blood in the veins, thus establishing the essential condition for hemorrhagic extravasation. The anemic necrosis that supervenes on the closure of the endartery naturally extends to the walls of the blood-vessels, which



Fig. 1.



Fig. 2.



consequently no longer are able to retain within the lumen the blood as it again enters, and so the red blood cells in masses pass through the walls—hemorrhage by diapedesis. This is confined mostly to the margins of the infarct, and the kidney is the most frequent seat of anemic infarcts with hemorrhagic margins. If the backward current passes through the whole infarct, then hemorrhage may take place throughout the whole extent of the latter, which then becomes a hemorrhagic infarct. Histologically this differs from the anemic infarct only in the presence of innumerable red blood corpuscles between the necrotic tubules and glomeruli; the other degenerative and disintegrative changes take place in both.

When an infarct exists for some time it diminishes in size. The external surface and the cut surface sink below the surrounding tissue, which in the earlier stages often is a little below the level of the infarct. At the same time the infarct becomes hard and dry. Histologic examination reveals that this is the result of a progressive disappearance of the necrotic tissue and a simultaneous "organization" of the area. The fat droplets in the necrotic and in part desquamated tubular epithelium increase in number and are subdivided in smaller and smaller particles, so that the necrotic tissue is emulsified and removed by absorption of the fat. The empty tubules collapse and become no longer demonstrable. Not infrequently there is a kind of regeneration of the uriniferous tubules, though only to a limited extent, in that new epithelial cells creep in along the basement membrane from the margins, and sometimes they inclose the loosened and necrotic epithelial debris in the lumen. The young cells are recognized as new epithelial cells by their numerous mitotic figures.

In the glomeruli there is also a desquamation of the dead epithelial cells, and a fatty disintegration of the masses in the capsular space; at the same time the capillary loops collapse. Not infrequently this collapse is prevented by extensive fibrinous deposition.

PLATE 78.

FIG. 1.—**Hemorrhagic Infarct of Kidney.** $\times 260$. The renal tissue wholly necrotic; only a few nuclei have taken the stain; the tubular epithelium to some extent desquamated. The intertubular spaces and the glomerulus at the upper right corner filled with thickly crowded red blood-cells.

FIG. 2.—**Margin of an Embolic Scar in the Kidney.** (Organized infarct.) $\times 50$. 1, Normal renal tissue; 2, contracted area once occupied by infarct containing glomeruli transformed into balls of fibrous tissue (3) and a few regenerated tubules.

As the leukocytic infiltration described before disappears through fatty changes and karyorrhexis a new permanent tissue grows into the infarct. Delicate vascular sprouts, surrounded and capped by young cells, rich in protoplasm and "epithelioid" in shape,—the so-called fibroblasts,—penetrate the area and spread throughout its whole extent, ultimately substituting the old parenchyma. The new tissue extends also into Bowman's capsules of the Malpighian bodies, but the globular shape of the latter is usually retained. As the vessels close and the cells diminish in number, while the fibrillar elements of the new tissue increase, there forms a dense fibrous tissue, which leads to considerable shrinking at the site of the infarct and constitutes the "embolic scar." It consists of more or less cellular connective tissue in which occur occasional heaps of round cells and concentrically fibrillated globules that correspond to changed Malpighian bodies. These masses lie very close together in the shrunken scar tissue because the intervening parenchyma has disappeared, and at first sight it appears as if the glomeruli had been greatly increased in relative number (Plate 78, Fig. 2). At the margins may be found the regenerative changes referred to in the foregoing, in form of narrow coils clothed with a low epithelium. The scar tissue always has less volume than the tissue it replaces, and on this account the fully organized infarct always appears as a funnel-shaped depression.



Fig. I.

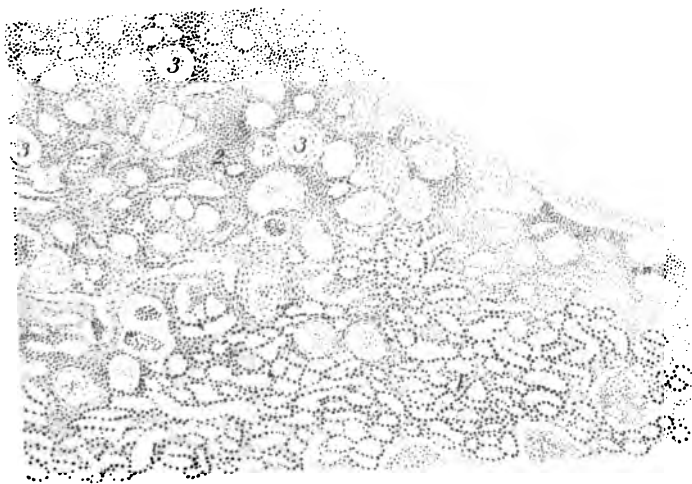
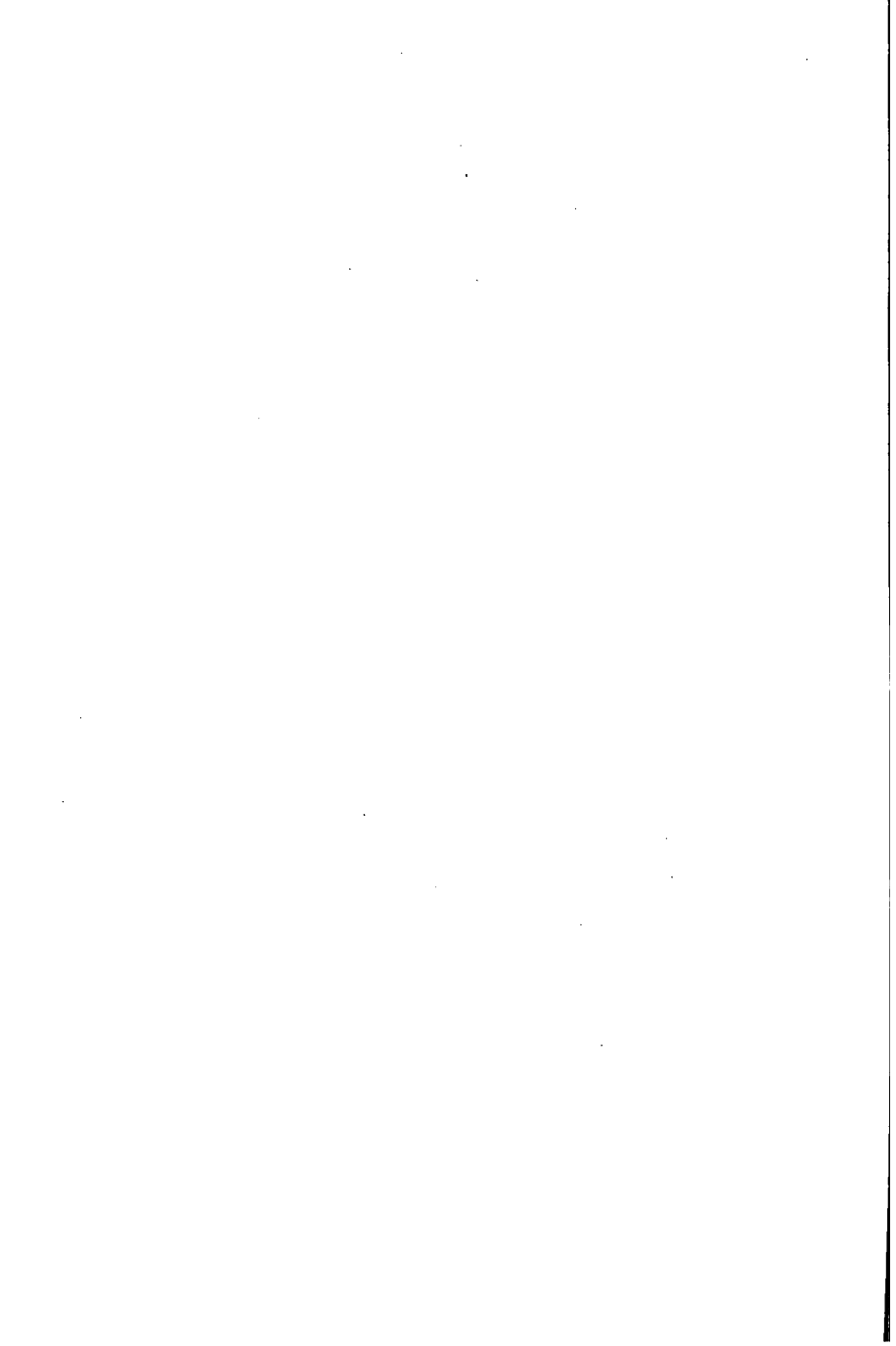


Fig. II.



The consequences so far described are the purely mechanical results of embolism, as may be produced by detached pieces of marantic thrombi or of degenerated areas in the walls of larger vessels. The process is different when inflammatory agents, such as living micro-organisms, are carried into the kidney by the emboli. The most frequent micro-organisms are staphylococci, streptococci, and pneumococci, and they may enter the kidney from endocardial vegetations or purulent venous thrombi. The further course of events varies according to the number and the virulence of the microbes ; the histologic picture is dominated, however, by the results of the chemotactic influences of the organisms, namely, the accumulation of pus corpuscles. Only in the earliest stages is it occasionally possible to demonstrate the cocci in endarteries or in capillaries. The glomeruli are the most suitable points for this purpose (Plate 90, Fig. 2), for the glomerular loops may be distended as if injected with cocci or parts may show varicose dilatations produced by heaps and sausage-shaped masses of bacteria. At the same time, there are usually single micro-organisms or swarms of such in the surrounding tissue and in the capsular space. Cross-section of small arteries may show confluent coccal masses. A dense zone of leukocytic infiltration rapidly forms around the micrococcal embolus. This is the embolic abscess of the kidney. In the cortex it is usually rounded and surrounded by a hemorrhagic border, while in the medullary pyramids the abscess tends more to assume a long and narrow form, so that when many are present converging lines run toward the apex.

Microscopic examination shows in the center a small arterial vessel filled with a mass of cocci, or a glomerulus the loops and capsular spaces of which contain micro-organisms (Plate 89, Fig. 2). About this focus is a dense infiltration of leukocytes, in the central parts of which the kidney tissue is no longer visible ; but at the outer margins of the infiltration the leukocytes are seen to enter first

the spaces between the tubules, whence they enter the tubules, pushing the epithelium away from the basement membrane. Cross-sections of uriniferous tubules may show complete desquamation of the epithelium, the lumen being filled with thickly massed leukocytes. At other places the epithelium may be adherent, but without nuclei and necrotic.

In the medullary pyramids the foci are somewhat different. The center is formed by one or more masses of cocci, but close study shows that they do not lie in blood-vessels, but in the lumens of urinary tubules. Often the cocci adhere to the surface of a granular or epithelial cast. It is therefore plain that these are micro-organisms which have passed through the vascular loops of a glomerulus into the capsular space, and further on in the urinary tubules until their excretion was arrested by some obstacle, usually a cast. A spindle-shaped, necrotic, unstainable zone forms around the mass, outside of which there is leukocytic accumulation. Much more rarely the medullary foci also start in emboli that close up an artery or a capillary in the medullary substance.

In all such "infectious," "mycotic," or "malignant" infarcts the acute inflammatory phenomena predominate over the purely mechanical and necrotizing results; and this the more, the larger the number of micro-organisms carried in.

Erroneously certain depositions of elements not of cellular nature are also designated as infarcts. These substances are not carried by the blood-vessels directly to the point of excretion, their presence in the kidney is not the result of embolism, and there is usually no necrosis of tissue; for it concerns the excretion by the glomeruli or the secreting epithelium of the uriniferous tubules of elements originally circulating in the blood and its precipitation and deposition along the route of elimination. In order to distinguish these deposits from embolic infarcts they have been designated as concrement infarcts. Various sub-

stances which enter the circulation may be deposited in the tubules of the kidney.

Under the influence of agents which destroy blood corpuscles the so-called hemoglobin infarct may form in the kidney. This consists of blood pigment which, circulating in the blood, passes through the glomeruli and the capsular spaces into the uriniferous tubules, and here is deposited mostly in the straight tubules, especially in Henle's loops and in the medullary pyramids. In the latter it forms large cylindrical masses. More rarely the capillary loops of the glomeruli are filled. The pigment appears in the form of brown, rounded and angular flakes, often of the size and form of red blood cells, but considerably darker in color. Hemoglobin infarcts are encountered after severe infectious diseases, especially scarlet fever; oftener still after the destruction of red cells in cutaneous burns or in transfusion of heterologous blood; also in certain intoxications, of which potassium chlorate intoxication must be mentioned first; but arsenic, phenol, pyrogallol, and mushroom poisoning (*Helvella esculenta*) also produce such deposits (Plate 79, Fig. 1).

In newborn children, especially those markedly icteric, there may be found in the uriniferous tubules, particularly of the medulla, cylindrical masses, which give Gmelin's reaction for biliary pigment in a characteristic manner. Potassic hydrate is added to the microscopic preparation, washed off with water, and followed by nitric acid; the masses now appear at first green, then blue, violet, and finally red. The epithelial cells of the tubules and the smaller blood-vessels occasionally contain granules of this substance. The condition is called bilirubin infarction.

Also in the newborn, but much oftener than bilirubin infarction, there is a deposition of urates in the lower ends of the uriniferous tubules. This is the uric acid infarct. It is found oftenest in children dying during the two first days of life, but occurs occasionally also in nurslings of a few weeks. Formerly it was regarded as a sure sign of

PLATE 79.

FIG. 1.—From the Renal Medulla in Poisoning with Potassium Chlorate. $\times 220$. The straight tubules for the most part filled with voluminous cylinders of disintegrated red blood corpuscles and confluent masses of hemoglobin. The lumens of the tubules dilated in places.

FIG. 2.—Uric Acid Infarct in the Kidney of the Newborn. $\times 25$. A papilla in which most of the papillary ducts are distended with greenish concretions (urate of ammonium).

extrauterine life, but it is found once in a while in still-born full-term fetuses. The medullary pyramids present fine yellowish-white to orange-yellow striations that diverge from the apex toward the base. Pressure on the papillæ brings out a powdery mass at the orifices of the papillary ducts, and microscopic examination shows that the straight tubules, especially in their lower part, are sometimes considerably dilated and filled with a coarsely granular greenish material pressed into cylindrical masses. High powers may reveal dark granules and small globules covered with sharp points. On the addition of acetic acid there appear crystals of uric acid. The amorphous deposits consist largely of ammonium urate (Plate 79, Fig. 2).

In uric acid diatheses and in arthritics, occasionally also in leukemia, precipitations of sodium urate take place in the kidney. As in the articular cartilages (Plate 120, Fig. 2), it forms needle-shaped crystals sometimes arranged in bundles. The renal parenchyma in the neighborhood, and often for some distance away, appears necrotic, and the borders of the areas are infiltrated with leukocytes ("gouty kidney").

Often pigments of various kinds, both endogenous and exogenous, are excreted by the kidney in which they may accumulate (see "Atlas of General Pathologic Histology," "Pigmentation").

In old age, especially in cachectic conditions, and associated with general atrophy of the kidney, there may be a

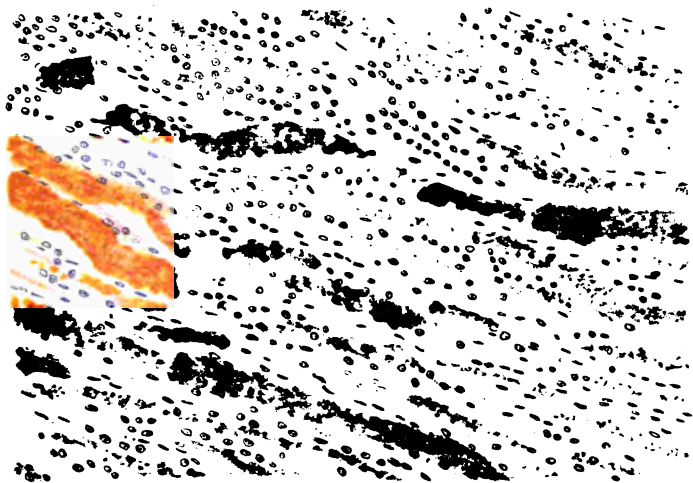


Fig. 1.

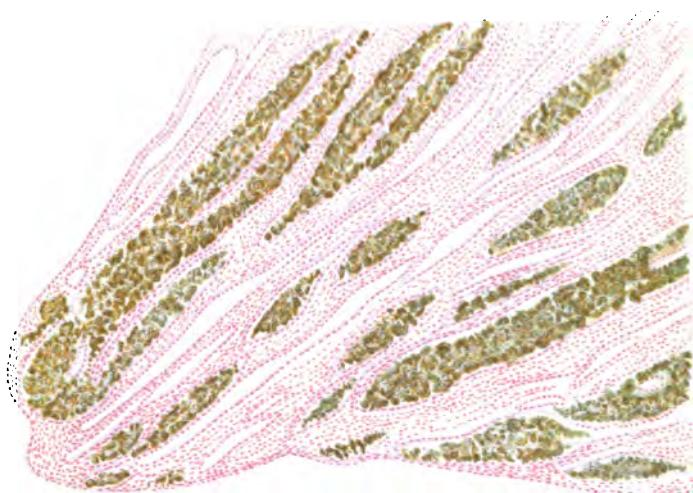
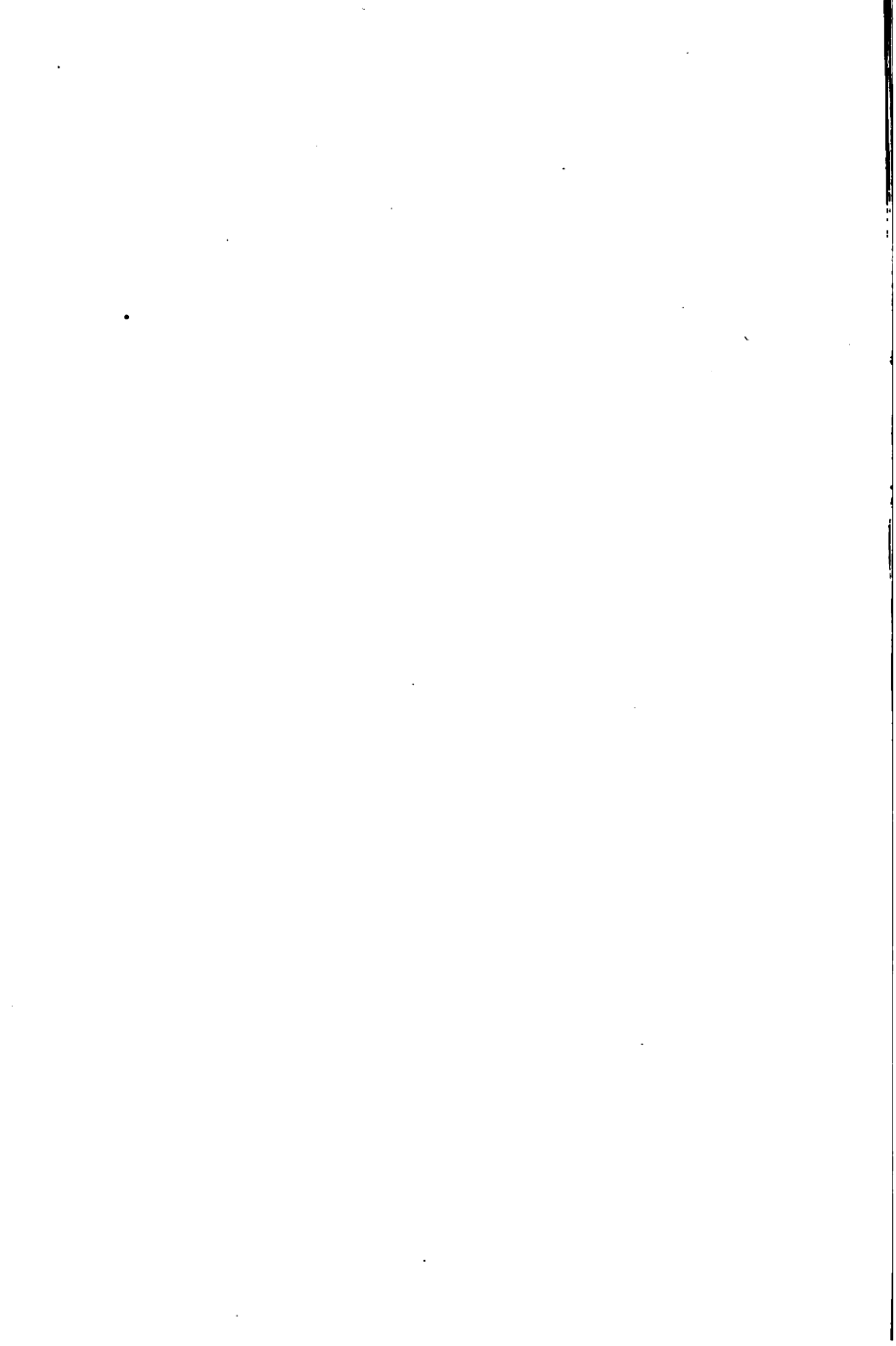


Fig. 2.



brown pigmentation of the epithelium of the convoluted tubules and of the loops—a “brown atrophy” quite analogous to that of the heart and the liver. The pigment is free from iron and forms fine particles about the nuclei of the shrunken epithelial cells.

In general icterus the kidneys are usually involved to a high degree. The biliary pigment is not uniformly distributed, but is found grouped in smaller areas of tissue in the form of fine yellowish or greenish clumps and flakes in the desquamated epithelium of the convoluted and straight tubules (Plate 80, Fig. 2). Epithelial casts loaded with pigment masses are found in the straight canals, and hyaline casts are sometimes diffusely stained by greenish biliary pigment (icteric cylinders).

Marked icterus of the kidney is nearly always associated with more or less extensive fatty changes in the renal parenchyma.

Pathologic pigment formations in the body are also often followed by elimination of the pigment through the kidneys and by deposits in the excretory ducts. In generalized melanosis and melanuria the kidneys are often of a smoky gray or deep brownish-black color. In teased specimens isolated glomeruli show a brownish, finely granular pigment in the capillary loops and in the capsular space, and the cells of the uriniferous tubules may be filled with pigment granules without the necessary presence of metastatic tumors or of severe parenchymatous degeneration. Sections often show the entire circumference of the uriniferous tubules quite uniformly infiltrated with pigment at the same time as the nuclei stain well (Plate 80, Fig. 1).

Finally, exogenous pigment introduced into the body as foreign substances may be deposited in the kidneys in the process of elimination. A classical example is the so-called silver infarct or argyria of the kidneys, which was seen more frequently in the past when certain diseases, as tabes, were treated for long periods with large

PLATE 80.

FIG. 1.—Melanosis of the Kidney in General Melanosarcoma. $\times 150$. The epithelial cells of the majority of the tubules are filled with brownish, finely granular pigment. Pigment masses in the lumen of some of the tubules and also in the interstitial tissue (right lower corner).

FIG. 2.—Icterus of Urinary Epithelium. $\times 160$. A few tubules contain desquamated epithelium filled by dark brown pigment.

FIG. 3.—Isolated Uriniferous Tubule in Cloudy Swelling of Kidney. Fresh teased specimen. $\times 300$. The epithelial cells are greatly swollen, the outlines and nuclei obscure, the protoplasm filled with masses of dust-like granules (albuminous).

doses of silver salts. By reduction, metallic silver is set free in the form of most minute black granules, which are deposited in the cortex of the kidney, as well as elsewhere, the glomeruli becoming visible macroscopically as small black points, while occasional grayish or black stripes appear in the medulla. Microscopic sections may show the glomeruli wholly covered with silver, which appears as fine granules, partly in the cement of the vascular epithelium, partly in the basement membranes of the glomeruli, and also of the uriniferous tubules. The nuclei appear normal. In the medulla there may form an exceedingly fine, delicate black network, corresponding to the course of the capillaries (see illustration in "Atlas of General Pathologic Histology," "Pigment").

Calcareous salts are deposited in the kidney under various conditions. In the first place, the salts in solution in the blood may be precipitated in the kidney in consequence of increasing concentration of the solvent; and, secondly, calcification may occur in necrotic renal tissue. The former occurs in the calcification of old age, in which the collecting tubules of the medulla are involved especially. In old people, and particularly in cachectic individuals, fine whitish converging lines are found about the medullary papillæ; the cribrum may be wholly incrustated, the open-

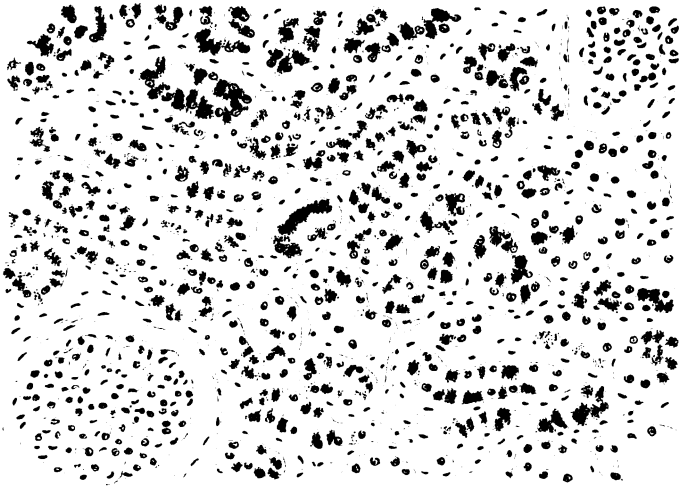


Fig.1.

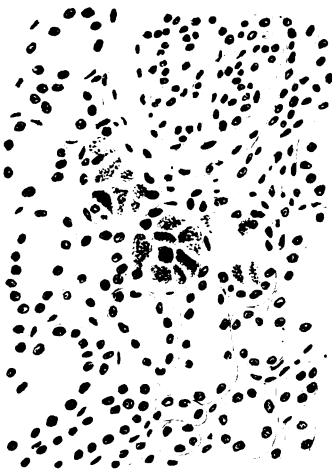


Fig.2.



Fig.3.



ings of the papillary ducts appearing as small holes. More infrequently this senile calcification extends higher into the straight tubules and into the medullary rays. In the affected areas the epithelium of the tubules is usually flat and atrophic, the lumen filled with whitish, glistening, scaly masses. On the addition of pure sulphuric acid these masses are dissolved at the same time as gas bubbles form, the salts being mostly carbonate and phosphate of calcium; and after a certain time fine rhombic and needle-shaped crystals are formed (gypsum), which, like tyrosin crystals, arrange themselves in bundles and radiating masses.

Similar calcareous deposits occur in the kidney, the medulla especially, in severe diseases of the skeleton associated with absorption of lime salts from the osseous tissue, as in osteomalacia and extensive caries.

Calcareous infiltration may succeed degenerative changes of the renal tissue in the course of certain intoxications, more particularly corrosive sublimate poisoning the fatal result of which is delayed for some days. This has been observed also in intoxications with bismuth, glycerin, phosphorus, and aloin. The calcification, which is often extensive, affects principally the cortex, and here the tubuli contorti and the straight tubules of the medullary rays. Macroscopically there may be seen fine, white, opaque flecks. The unstained microscopic preparations examined in direct light show in the labyrinths extensive scales and granules, which have a peculiar white glitter. The solution with gas formation on the addition of sulphuric acid, and the rapid formation of gypsum crystals, show that these are calcium salts.

The best general view is obtained in sections stained with hematoxylin. The epithelium of the convoluted and straight tubules is necrotic over extensive stretches, anuclear, lifted from the basement membrane, irregularly split up, filling the lumen in the form of separate scales or as continuous cylinders. Occasional nuclei persist, but these

PLATE 81.

Acute Fatty Degeneration of Kidney in Pregnancy. Frozen section. Sudan staining. $\times 680$. All tubules greatly swollen; the epithelium filled with fat droplets stained red by sudan. The inner layers of the cells in part free from fat. The glomerulus normal. At 1 desquamated cells with fatty changes in the capsular space.

are usually pushed into the basal parts of the cells (Plate 83, Fig. 1). The light blue necrotic cell masses contain in places deep blue spots, which with high powers are found made up of single granules and globules. In the tubules of the medullary rays entire cylinders are found, consisting of calcareous masses. The glomeruli are mostly free from special changes.

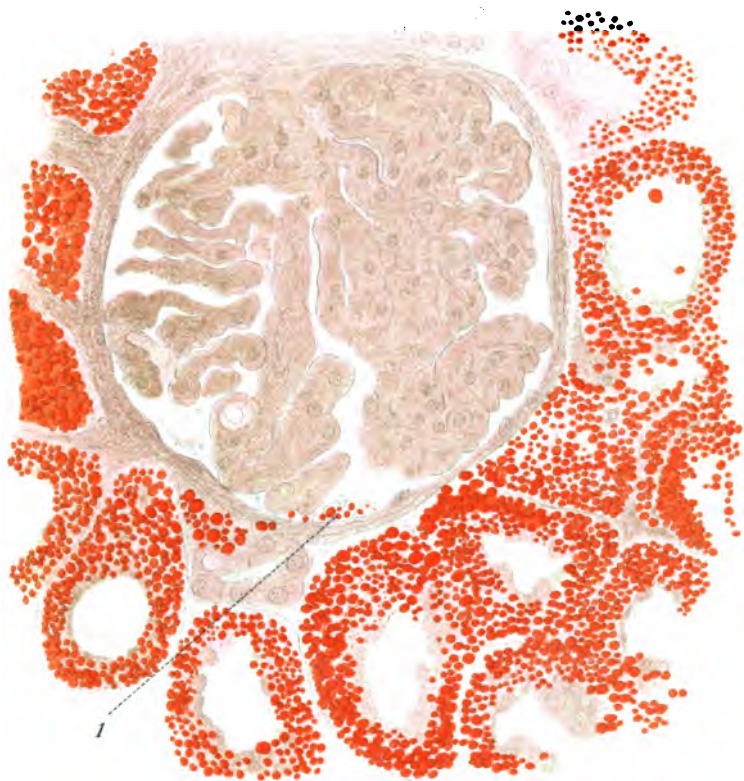
Secondary calcareous infiltrations occur in the kidney after extensive shrinking and connective-tissue formation, and with especial frequency in old embolic scars. The concentrically fibrillated connective tissue occupying obliterated glomeruli is often changed into glistening calcareous spheres.

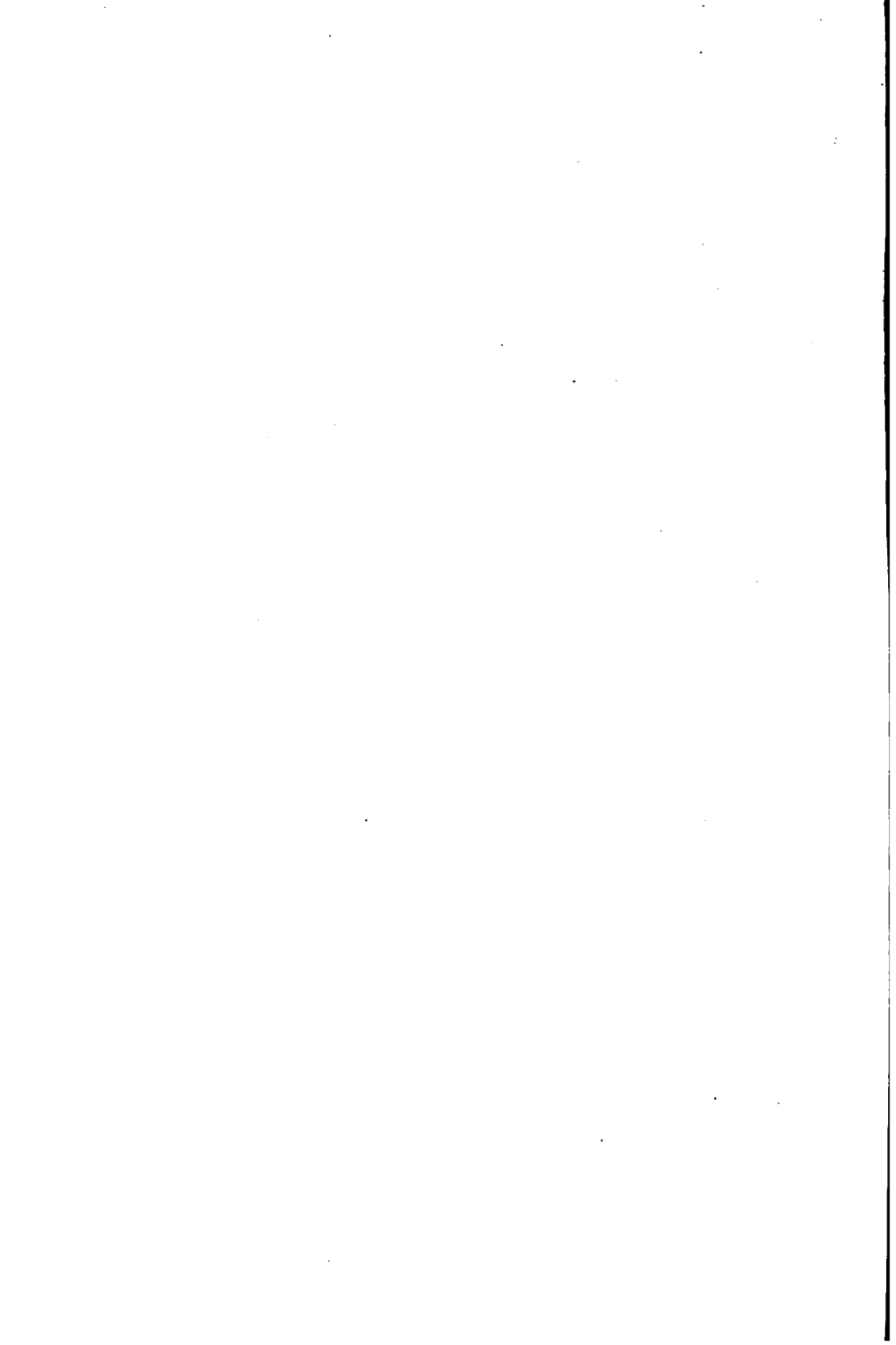
Degenerations.

Degenerations in the kidney are often associated with inflammatory changes, and while these two groups of changes are often dependent on each other, they may occur independently without any causal relationship. But even pure renal degenerations are manifest clinically by the presence of casts and of albumin in the urine, and the clinician generally regards these deviations from the normal as symptoms of renal inflammation,—“nephritis,”—so that many forms of pure renal degeneration are clinically regarded as inflammatory processes.

Cloudy Swelling or Albuminous Degeneration.

In the course of many infectious diseases in which albuminuria appears,—as in typhoid fever, variola, scarlatina, measles, pyemic and septicemic [bacteriemic] diseases,





cholera, pneumonia, etc., and in intoxications, especially in the early stages of phosphorus-poisoning and in poisoning with mushrooms, as well as with carbonic oxid, ethereal oils, and sodic bicarbonate,—there is anatomically a cloudy swelling of the kidneys. It may be produced experimentally in one kidney by tying a renal vein of the other kidney, and this observation led Virchow to regard cloudy swelling as the expression of “nutritive stimulation.”

The macroscopic appearances are very characteristic. The organ is enlarged, soft, of doughy consistence; on the cut surface the cortex is broadened, pale grayish-yellow, and swollen, the medullary pyramids being darker in color. Often the kidney looks as if acted on by hot water, and a turbid juice may be scraped from the cut surface.

Fresh frozen sections show that the changes are unequally distributed; not all the tubules in the labyrinth are involved, but first and foremost the tubuli contorti of the second order, and less so the other convoluted tubules and Henle's loops. The affected parts are distinguished from the surrounding tissue by their opaque grayish appearance. On isolation of such areas by teasing, the uriniferous tubules are found enlarged, the lumen nearly or wholly occluded, the individual cells greatly swollen, their borders indistinct or lost, and the inner aspect occupied by vesicle-like vacuoles. The cell contents are clouded, containing a mass of very fine, dust-like granules, so that the nucleus is not visible except when the section happens to pass straight through it. In the fresh preparation the single cells are easily teased apart. The cells are often lifted from the basement membrane, and may lie as flaky masses in the interior of the coils of the membrane. The cell outlines are irregular and indistinct. When acetic acid is added, the cloudiness at once disappears, the granules are dissolved, and the nuclei become very plain. The granules being soluble in acetic acid, and also in potassic hydrate, are consequently albuminous precipitate. The

nature of cloudy swelling therefore consists in an accumulation of fine albuminous particles in the epithelial cells.

In stained sections these characteristic appearances are not visible, because the albuminous granules become greatly swollen, in part wholly dissolved in the various solutions employed. Evidences of deep-seated disturbances are seen in a partial loss of staining affinity in the nuclei and in occasional disturbances in the continuity of the cellular lining, a "dissociation" of the epithelium of the urinary tubules, which leads to separation from the basement membrane and accumulation of cells in the lumen. In many places the lumens of the tubules are filled with a spongy structure of coagulated thready albuminous masses. Very thin sections of tissue fixed immediately after death show, when stained with Altmann's granula stain, that in cloudy swelling the normal cell granules are diminished and pushed into the inner parts of the cell body (Schilling), hence they are apparently not identical with albuminous granules. In well-fixed preparations regenerative changes associated with mitotic figures may be seen in the epithelium of the urinary tubules.

Fatty Degeneration.

Fatty degeneration of the kidney very often begins in cloudy swelling, so that in places a partial cloudy swelling may be associated with fatty changes. Fatty changes also frequently follow inflammatory alterations, or inflammation and fatty degeneration exist side by side. Pure fatty degeneration is found oftenest as the result of certain intoxications, especially those caused by phosphorus, arsenic, carbolic acid, and iodoform, as well as by poisonous fungi; also in severe nutritive disturbances in consequence of pernicious anemia, and frequently in pregnancy. The kidneys show striking and characteristic changes, such as enlargement, soft consistence, and light yellow color. The examination in water of sections made by freezing or by means of a double knife usually shows the change to be

quite uniform. The cortex is the part principally affected; the medullary substance is more rarely involved, and then in less degree. The convoluted tubules of the second degree are the parts especially implicated, and immediately subcortical, triangular opaque areas occur about the stellate veins (Ribbert). Dark opaque spots are seen also in the cortical pyramids, but the glomeruli appear as lighter spots. Under high powers the fat droplets are seen as larger and smaller refractive globules in the epithelial cells, which are more or less enlarged. In less advanced instances the outer parts of the cells near the basement membrane are filled with droplets, while the inner zones are free from fat, but with indistinct borders, as if in a condition of cloudy swelling (Plate 81).

In the highest grades of fatty degeneration the cells of the uriniferous tubules are filled with heaps of droplets, and the single droplets may run together and form larger globules.

The nuclei of the cells are usually covered over. The droplets do not disappear on adding acetic acid, and the nuclei become plainer only in the less affected parts. The lumen of the tubules often contain coagulated albuminous masses and cylinders of amalgamated, fatty epithelial cells. Such cylinders appear also in the urine under these circumstances, and the fat in them is demonstrated well by means of sudan III (Rieder). Fat droplets are also found at times in the epithelium covering the capillary loops in the glomeruli, and in desquamated cells from Bowman's capsule.

In advanced instances, as the result of absorption, fat also appears in the intertubular tissue about the vicinity of the vessels and in the perivascular spaces.

The best general view of the distribution of the fat and of its relations to the epithelium is obtained from sections that have been treated with sudan III or with Flemming's solution. In hardened sections mounted in balsam the fat is extracted [except in tissue fixed in Flemming's solution];

in place of the droplets there are numerous vacuoles, so that the tissue has a sieve-like appearance. In many places the nuclei are absent or deformed by pressure of the fat and pressed against the cell wall.

Secondarily fatty changes occur in many inflammations, in icterus, and in amyloid degeneration of the kidney.

Glycogen Degeneration.

In diabetes mellitus the epithelium of the tubules, particularly in the loops, contains deposits of drop-like masses colored brown with iodine gum. The cells are enlarged and swollen, the nuclei distinct. In order to demonstrate the deposits it is necessary to fix the tissues in absolute alcohol immediately after death.

Amyloid Degeneration.

In the earliest stages of amyloidosis the degeneration often occurs in the kidney only, and there may be as yet no degeneration in other parts of the body. The process is recognizable macroscopically in the earlier stages, and the appearances are easily understood from study of the minute changes.

The whole organ is pale, dry, somewhat friable, and enlarged. As elsewhere in the body, amyloid changes in the kidney also begin in the vessels, and more particularly in the glomeruli, which show the earliest traces of the process. In an early stage frozen sections of fresh tissue show a few glistening, homogeneous masses in the capillary loops of the glomeruli. On addition of tincture of iodine, these masses assume a dark mahogany-brown color. The convoluted tubules may contain a few fat droplets and occasional cylinders. In more advanced stages the alterations of the glomeruli become quite plain to the naked eye; larger than normal, they appear on the cut surface as peculiar, glistening, half translucent, prominent points. And in advanced cases the glomeruli appear as small

globular particles of translucent material deposited in the cortex.

Microscopically there is found to be an increase in the homogeneous material at the same time as the cells and the nuclei are correspondingly diminished. Large parts of a glomerulus may be filled entirely with large, homogeneous, glistening flakes that occlude the capillaries and eventually obliterate the entire glomerulus (Plate 82). Only a few flattened nuclei may remain. At times one capillary loop may be occluded, while the neighboring ones are normal or but little changed (Plate 82, Fig. 2). Cross-sections of the glomeruli also often show broad, homogeneous rings and loops the lumen of which is without epithelial lining. The degeneration also appears in other of the smaller arterial vessels as well as in the capillaries of the cortex and the medulla. In the arteries the change always begins in the muscle-cells of the media. The sections may show homogeneous rings between the uriniferous tubules that correspond to greatly thickened arteries and may cause pressure on the adjacent parenchyma. In teased specimens it is occasionally possible to isolate amyloid glomeruli with homogeneously thickened and narrowed vasa afferentia as far as the corresponding arteria interlobularis. In many cases all the cortical vessels above the arcus renales are amyloid.

In the most advanced cases the degeneration extends to the basement membrane of the uriniferous tubules and of the glomeruli, which become homogeneous and thickened, the tubular epithelium disappearing on account of compression. Amyloidosis never directly involves the epithelium, which becomes involved secondarily only. Thus, in addition to atrophy and attenuation of the epithelial cells, they often are the seat of a more or less extensive fatty degeneration. In certain instances it may seem as if amyloid degeneration of the kidney itself is secondary to chronic degenerative and inflammatory conditions in the kidney. In most cases renal amyloidosis depends on

PLATE 82.

FIG. 1.—**Amyloid Degeneration of Kidney.** Stained with iodine green. $\times 54$. 1, Glomeruli with amyloid capillary loops; 2, hyaline casts in urinary tubules.

FIG. 2.—**Amyloid Degeneration of a Renal Glomerulus.** $\times 280$. 1, Wholly amyloid capillary loops with greatly thickened walls and occluded lumens; 2, a capillary still permeable, the degeneration beginning in its wall.

the same factors as amyloidosis in general: namely, chronic pulmonary and intestinal tuberculosis, tuberculosis of bone with prolonged suppuration, cancer cachexia, and other exhaustive diseases.

The best pictures of the distribution of the process are obtained by staining frozen sections with the familiar aniline stains giving metachromatic effects (methyl violet, gentian violet, iodine green, etc.). But preparations so stained are not suited for the study of the finer structural relations, for which purpose hematoxylin and eosin, as well as van Gieson's stain, are preferable.

Inflammations of the Kidney.

In regard to no other organ is there such far-reaching divergence between the clinical and anatomic conception of inflammation as in the case of the kidney. In connection with the description of degenerations of the kidney it was pointed out that the degenerations are often associated with inflammation. But clinicians frequently designate as nephritis pure renal degenerations when initiated by the symptoms of albuminuria. Albuminuria occurs, however, in cloudy swelling and in fatty degeneration without any admixture of inflammatory processes, and these conditions are still frequently but erroneously designated anatomically as "parenchymatous nephritis." In all organs the interstitial tissue is predominantly involved in all inflammatory processes, which are hardly conceivable without

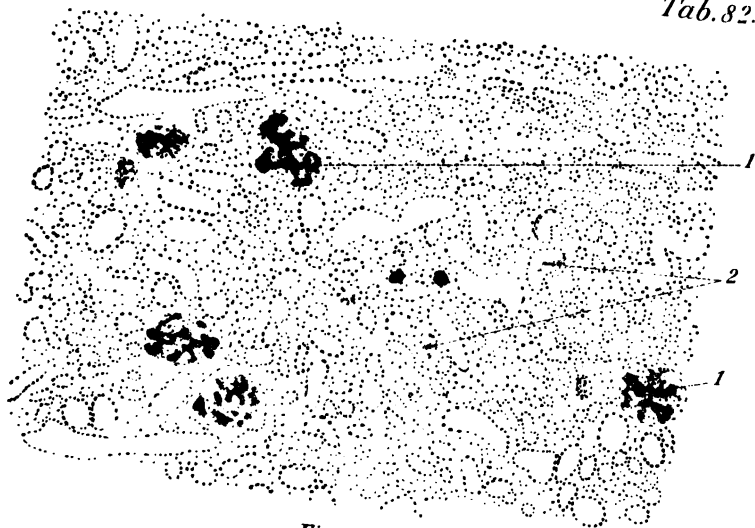


Fig. 1.

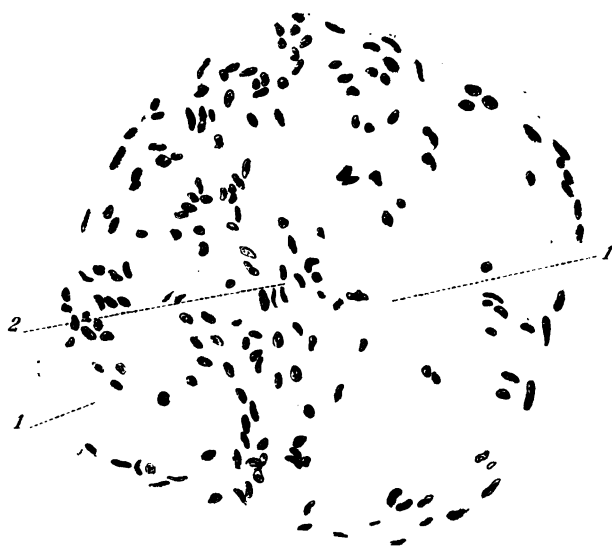


Fig. 2.

some participation by the interstitial tissue, because it carries the vessels from which the phenomena of inflammation in the last instance largely take their departure. As the expression "parenchymatous inflammation," and particularly "parenchymatous nephritis," has obtained a secure foothold, it ought at least to be reserved for certain forms of changes in the kidney in which, in addition to inflammatory changes, degenerative conditions also appear in the foreground.

From the anatomic and histologic standpoint it must be insisted that the diagnosis "nephritis" is justifiable only when the elementary processes of inflammation, such as exudation, emigration, and increased cellulation, are present. The anatomic picture of nephritis may be complicated in various ways:

1. The inflammation may run its course in the various structural divisions of the kidney, such as the uriniferous tubules, the glomeruli, and the interstitial tissue.

2. The changes in one of the localities mentioned may predominate greatly over the others.

3. The intensity and the extent of the inflammatory changes are subject to great variations.

4. And especially because in nearly all cases the purely inflammatory changes are combined with degenerative changes; and the latter may so predominate, either at certain stages or throughout the entire course, that they conceal the inflammation.

The degenerative conditions are later followed by the usual reparative and substitutive processes, and this renders the exact demarcation of the inflammatory area still more difficult.

From what has just been said in the foregoing it is quite clear that in the histologic description of inflammations of the kidney it is not possible to follow the usual, and clinically indispensable, division into "parenchymatous" and "interstitial" forms; but that all forms must be considered from the viewpoint of the doctrine of inflammation,

PLATE 83.

FIG. 1.—Calcareous Infiltration of the Epithelium of the Urinary Tubules in Sublimate Poisoning. Stained with alkaline hematoxylin. $\times 320$. The epithelium of the tubules nearly all necrotic, largely devoid of nuclei, and loosened from the basement membrane. In many cells are deep blue granules of lime salts.

FIG. 2.—Acute (So-called Parenchymatous) Nephritis. $\times 100$. 1, Urinary tubules with swollen, partly necrotic epithelium without nuclei; 2, round-cell accumulations in the interstitial tissue; glomeruli more cellular than normal.

and as distinguishable the one from the other only by the predominance of this or that inflammatory phenomenon. In other words, there is no essential difference between the various forms of nephritis but those of degree and period of development. It will be found advantageous to separate the acute processes, and those that reach the height of anatomic evolution in a brief time, from others which develop more slowly. As the latter forms always lead to more or less extensive interstitial proliferation and simultaneous destruction of renal parenchyma, they may be placed in a separate group as "productive interstitial nephritis."

Acute nephritis may present itself in forms that are clearly capable of "restitutio ad integrum"; but in other cases the lesions, without pause, lead to progressive destruction of the organ, accompanied usually with new connective-tissue formation. Since John Bright first correctly understood the nature of the latter disease of the kidney, it has generally been called Bright's disease (*Morbus Brightii*), and various stages are distinguished, according to the development of the process.

Considering first the forms of acute (so-called "parenchymatous") nephritis, which develop in consequence of numerous harmful influences of hematogenous origin, and especially in connection with the various infectious diseases of all kinds, it is found that the kidney appears larger

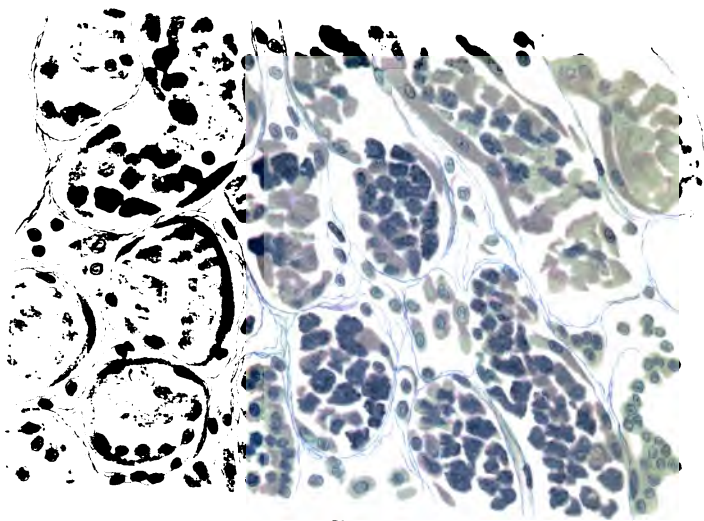


Fig. 1.

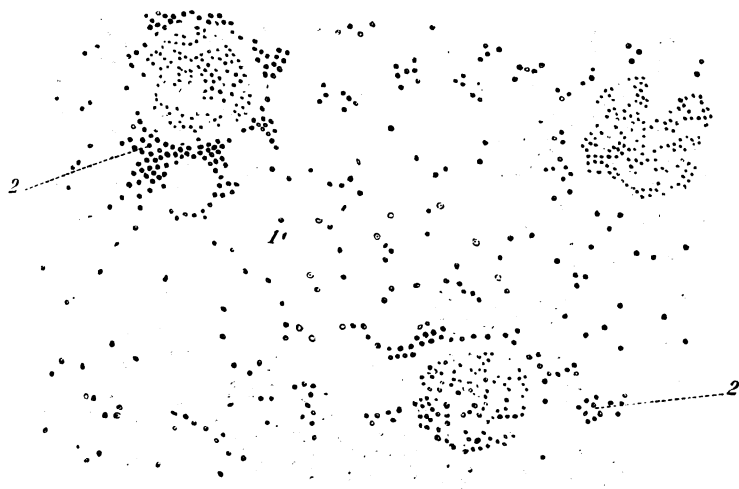


Fig. 2.

than normal and softer, the lessened consistency being especially noticeable in the cortex. The cortex on the cut surface appears irregularly flecked, swollen, broadened, and traversed by homogeneous areas. Frozen sections of pieces subjected for a few moments to boiling water give a good picture of these initial changes: the uriniferous tubules appear more widely separated than usual, the intertubular vessels may not seem especially congested, but the interstitial tissue is swollen and edematous, the fine connective-tissue fibers and the walls of many vessels evidently thickened. At various points, but especially about small subcortical veins, there may be accumulations of round cells with small, deeply stained, round or lobulated nuclei—hence either lymphocytes or leukocytes. In these preparations the contents of the uriniferous tubules and of the glomerular capsules appear changed especially (Plate 84, Fig. 1). They may consist of coagulated filamentous or homogeneous albuminous masses, in which fibrin may be demonstrated in the form of threads, which, stained blue by Weigert's method, run through the coagulated masses or are mixed with the contents of the capsular spaces. In places leukocytes with fragmented nuclei may be found in the interior of the uriniferous tubules. There are here undoubted inflammatory changes, such as exudation and emigration of white blood cells. Finer sections subjected to nuclear and protoplasmic stains (Plate 84, Fig. 1) show changes in the epithelium of the tubules also. In the various parts of the labyrinths—tubuli contorti and Henle's loops—the epithelium seems loosened from the basement membrane; in many places an actual desquamation has taken place, and single cells lie in heaps in the apparently widened lumen, or they have coalesced into denser masses in which single cells are no longer recognizable, the tubules being seemingly filled with giant cells. Desquamated epithelial cells and leukocytes may occur side by side or they may be molded together into cylindrical casts. Here and there are stretches of membrana

PLATE 84.

FIG. 1.—**Acute (Parenchymatous) Nephritis.** $\times 200$. Tubules dilated, epithelium in many places loosened. Cell outlines indistinct. In some places the interstitial tissue and the lumens of the tubules contain heaps of leukocytes with deeply stained, fragmented nuclei.

FIG. 2.—**Subacute Nephritis.** $\times 100$. Tubules dilated, epithelium low, lumen containing coagulated albuminous masses. Intertubular tissue everywhere uniformly widened, containing numerous spindle-shaped and round nuclei.

propria without all trace of cellular lining. In other cases, especially after some time, the epithelium in some portions of the tubules becomes low and short, while in other places the cells, though of normal length, and perhaps enlarged, have lost the cilia or striæ upon the free ends, which project into the lumen in an irregular manner. From the epithelial desquamation this form has been called also desquamative or catarrhal nephritis. Isolated fresh cells from cases of this kind show cloudy swelling of the epithelium, often combined with a moderate fatty change. In well-stained and thin sections it is made out easily that it concerns not merely simple desquamation with secondary destruction, but real proliferative processes in the epithelium; for mitotic figures are found often in the still adherent cells, and sometimes many figures are seen in a single cross-section of tubules.

Edema of the interstitial tissue and exudation of an albuminous fluid into the urinary tubules, and especially into the capsules of the glomeruli, and emigration of white corpuscles into the intertubular tissue and through the glomerular loops into the urinary tubules, are, then, the characteristics of these forms of nephritis.

The Malpighian bodies may remain quite intact, showing no changes except deposits of albuminous material, best demonstrated by the method of boiling. If the accumulation of leukocytes in the tubules increases, then the glomerular capillaries naturally contain such cells in

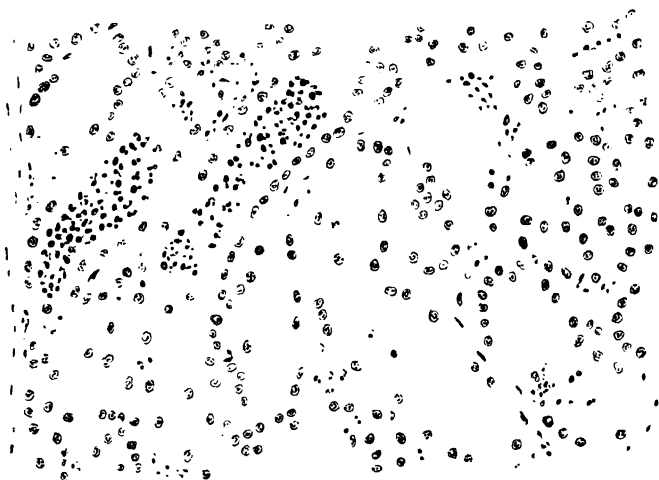


Fig. 1.

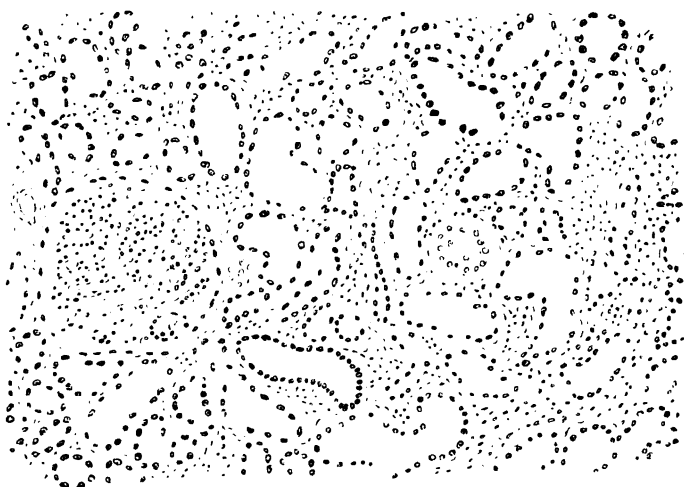
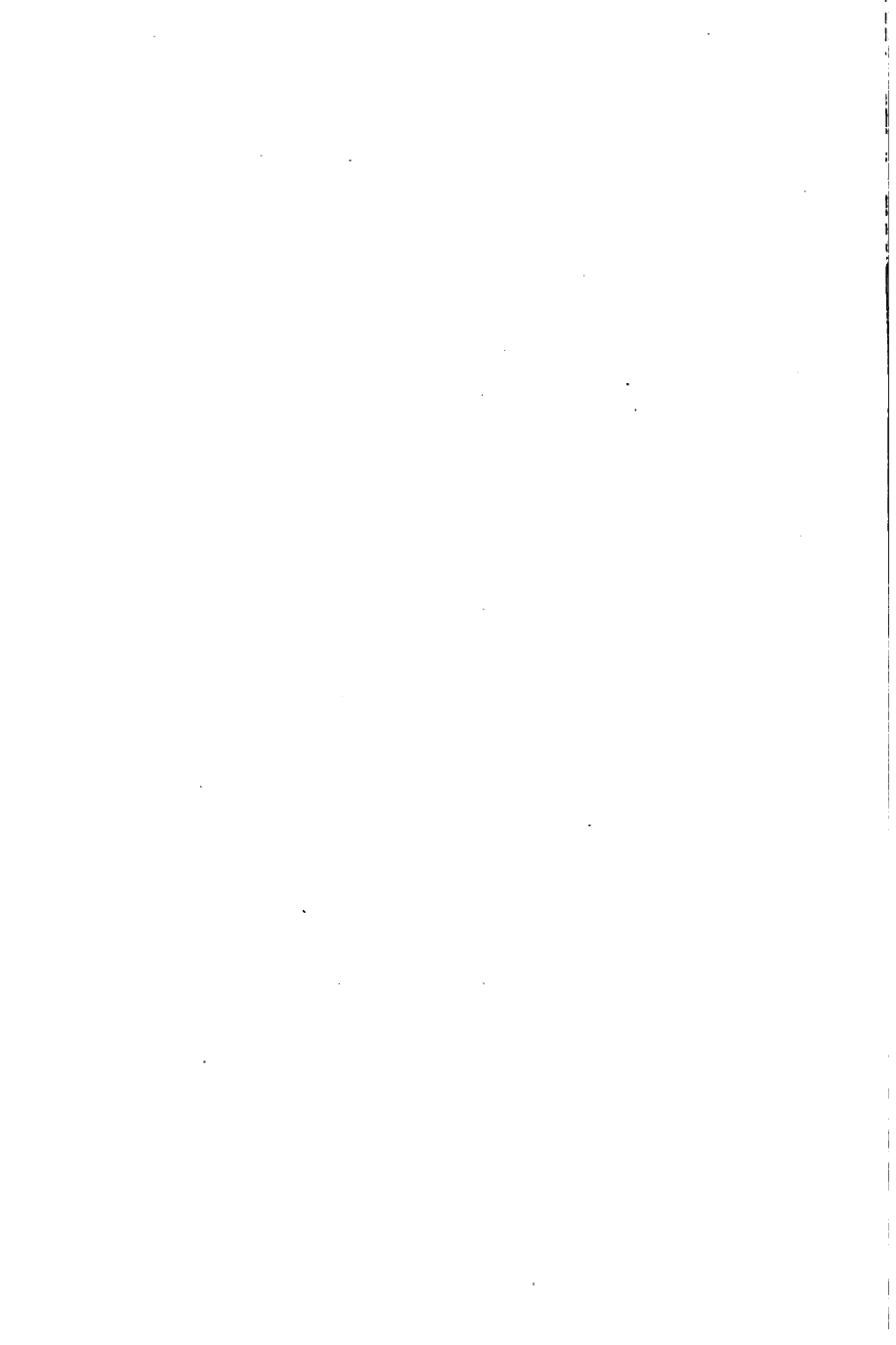


Fig. 2.



greater number. In some cases, especially after certain infectious diseases, among which scarlet fever stands first, the glomeruli are the first and the most seriously involved in the acute renal inflammation. According to the investigations of Ribbert, very many, if not all, forms of this nephritis are introduced by glomerular alterations. These forms are referred to as "glomerulonephritis," which is characterized especially by the following changes: By boiling it is often possible to demonstrate in the capsular spaces large quantities of albumin, which may appear as rings surrounding the whole capillary tuft, which is crowded away from the capsule, or as half-moon-shaped masses extending to the vascular stem. In suitable sections the extension of coagulated albumin may be followed from Bowman's capsule into the beginning of the convoluted tubules. Numerous admixtures may result, such as fibrin, which is rarely present; more often, red blood cells; and still oftener, white blood cells, but especially desquamated epithelial cells from the lining of Bowman's capsule and from the epithelial covering of the capillary tuft. The glomerular capillaries are often filled with red corpuscles and single capillary loops are rendered very prominent. Often the red corpuscles are mixed with such an excessive number of leukocytes that single loops, and even entire glomeruli, appear plugged with densely massed leukocytes. Under these circumstances the glomerulus, even under low magnification, appears richer in nuclei than normal. At the same time the walls of the vessels may show a peculiar degeneration, become thickened and homogeneous, and flakes of material staining deeply with anilin dyes project into the lumens. This alteration is designated as hyaline degeneration of the capillary loops, which thereby are partly or completely obstructed; this, in turn, favoring further stagnation of the contents and the formation of thrombi.

The epithelium covering the tufts, as well as that lining Bowman's capsules, gives the same evidences of prolifer-

ation as that of the urinary tubules. Epithelial cells are continuously exfoliated into the capsular space, where they may accumulate into concentrically lamellated masses that surround the glomerulus and appear as rings or as half-moons, like the albuminous exudations referred to. In fine sections cells may be seen adherent at one end or by one surface to the glomerulus, while the rest projects into the capsular space. As in the uriniferous tubules, single mitotic figures are often found in the remaining epithelial cells. The basement membrane of Bowman's capsule not infrequently shows a thickening and a peculiar concentric fibrillation, which will be referred to again.

In many cases of acute and subacute nephritis, especially after scarlatina, the glomerular changes, often referred to as "glomerulitis," associated with more or less albuminous exudation into the urinary tubules, are the only anatomic alterations of a clinical nephritis with pronounced symptoms.

[In infectious diseases, especially of children, there often occurs an acute interstitial nephritis, characterized more particularly by focal and more general infiltrations of plasma cells, lymphoid cells, polymorphonuclear and eosinophilous (Howard) leukocytes. Accumulations of a focal character are especially apt to occur at the boundary zone of the pyramids, in the subcapsular regions, and around glomeruli. Acute interstitial nephritis of this type has been studied thoroughly by Councilman ("Jour. Exp. Med.," 1898, III, 393-420), whose observations are confirmed by Howard ("Amer. Jour. Med. Sci.," 1901, CXXI, 151-163).]

Acute Hemorrhagic Nephritis.

Hemorrhagic inflammations of the kidney, often combined with profound degenerative changes, are observed especially in various forms of hematogenous damage to the organ, as in septic and pyemic [bacteriemic] processes, in ulcerous endocarditis, in puerperal sepsis, and in anthrax.

Macroscopically the kidney is large, soft, and mottled with numerous dark red points and stripes in the pale gray parenchyma, present also, at times, here and there in the medullary substance as far as to the papillæ. The glomeruli are usually exceptionally prominent on the cut surface, and often project as deep red points and globules.

The microscope also shows that the process does not involve the whole parenchyma uniformly, but mostly in spots. The cortical and subcortical vessels are greatly dilated and filled with red blood corpuscles. Often there are lesions of the vascular lining, exfoliated epithelial cells lie among the red blood corpuscles, and continuous epithelial lamellæ may be separated.

In the interstitial tissue there are often extensive accumulations of red corpuscles, intermixed with small groups of round cells, especially in the vicinity of the smaller veins. The hemorrhages are evidently the result of tears of the vessels in the stroma. As indicating the vascular changes may be taken the presence of red corpuscles between the separated layers of the walls of the vessels and in the lymphatic spaces of the adventitia. Deposits of fibrin are often present in the form of graceful networks between the red corpuscles. The glomeruli show extreme congestion. The capsular spaces may not be visible. Very often numerous blood corpuscles pass through the capillary loops and accumulate in the capsular space as large rings of blood at the same time as the epithelial cells undergo desquamation. Among the red corpuscles and epithelial cells may be fine threads of fibrin. Numerous capillary loops are the seat of hyaline thrombosis with simultaneous loss of the vascular epithelium.

In many places the uriniferous tubules appear filled with blood. In the convoluted portions the red blood corpuscles are still fresh; further down in the straight tubules they are packed into denser heaps and cylinders, often stained diffusely with hemoglobin, in which it is difficult to recognize individual cells. The blood casts

may be mixed with desquamated and in part necrotic epithelial cells. By the various accumulations the lumen of the uriniferous tubules in general is dilated, especially the convoluted divisions, which are crowded with blood cells, and the epithelium is pressed together and appears flat and low.

Frequently the epithelial lining of the uriniferous tubules is separated, often in continuous layers, and the cells are mixed with the blood. But even when present, it is not closely attached to the basement membrane, as red corpuscles penetrate between the latter and the cellular lining. This may take place throughout the whole circumference of the tubule, so that cross-sections show upon the basement membrane a continuous layer of red corpuscles, covered by the folded, compressed, and detached epithelial layer. Here and there red blood corpuscles are seen within swollen epithelial cells. Regenerative processes are betokened under these circumstances also by the presence of mitotic figures.

If the process is continued for a longer time, red corpuscles in the tissue spaces may change into pigment masses, which are found especially in the interstitial tissue and in the thickened perivascular sheaths. The blood corpuscles within the uriniferous tubules are eliminated as such or after they have been compressed into cylinders.

The Subacute and Chronic Inflammations of the Kidney.

Inflammatory processes in the kidney of longer standing all lead to productive changes in the interstitial tissue, but there are often important differences in the conditions of the uriniferous tubules and the glomeruli. If these are well preserved, while much connective tissue has formed between them, so that the interstices are broad and the parenchymatous parts widely separated, then the macroscopic result of the change will be an enlargement of the organ. But if the uriniferous tubules, and also the glomeruli, have been destroyed to a considerable ex-

tent, and simply substituted by connective tissue, which naturally tends to cicatricial contraction, then the kidney will be found small and hard. There are also differences that depend on the distribution of the process, whether uniform throughout all parts of the organ, or circumscribed and focal, the contraction leading to depressions at the points of parenchymatous destruction, while the relatively intact parts form elevations.

In considering the form of nephritis which develops after continued existence of the inflammatory conditions just outlined, it is worthy of note that the regenerative capacity of the epithelium is quite considerable, and that repeated shedding of the epithelial lining of the tubules may be followed by a new layer of cells. Hence the condition of the glomeruli is of much importance: when the exudation, cell proliferation, and disintegration of the exfoliated epithelium reach such an extent that the capillary loops suffer damage and become occluded either by hyaline thrombosis or by compression of the exudate, then the uriniferous tubule emerging from the glomerulus is deprived of its function, it becomes atrophic from inactivity, and its cells break up into fatty detritus. But if the glomeruli are in good condition, then the water separated by them washes out the desquamated epithelial cells, the albuminous masses, and the casts in the uriniferous tubules, and the epithelium of the latter may regenerate. It is plain that extensive and severe early glomerular lesions lead to more rapid degenerative changes, followed by cicatricial contractions, if time is given; whereas if the glomeruli are but little affected or quite intact, even marked degenerative and exudative parenchymatous changes may be borne quite easily for a relatively long time.

In the latter instances there is desquamation of the tubular epithelium, granular disintegration, cast formation, and exudation of albuminous masses into the lumens of the tubules. In the end the regenerated epithelium does

PLATE 85.

FIG. 1.—**From a "Large White Kidney."** $\times 300$. The epithelium of the urinary tubules everywhere separated from the basement membrane; the cells appear frothy, many have lost their nuclei, and the tubular lumens contain shed cells and albuminous masses.

FIG. 2.—**Chronic (Parenchymatous) Nephritis.** $\times 160$. Tubules same as in Fig. 1. In many there are homogeneous or hyaline casts; interstitial tissue broadened in places.

not reach the height nor the size of the original, but remains flat and low, often almost like endothelium (Plate 84, Fig. 2), and the lumen of the tubules appears wider than normal, although no real increase in the diameter of the tubules may have taken place.

The interstitial tissue in such cases is usually considerably increased. In the place of the groups of round cells and of the swollen interstitial tissue are found larger young connective-tissue cells,—spindle-shaped fibroblasts,—interspersed with but few round-cell accumulations (Plate 84, Fig. 2). Naturally, this causes an increase in the size of the kidney. And in consequence of the continued fatty changes in the epithelium and the compression of the blood-vessels, the organ generally is pale in color—the "large white [or yellow] kidney." Scattered hemorrhages may give the external and the cut surface a mottled appearance—the "large mottled kidney." In these cases the surface

PLATE 86.

FIG. 1.—**Acute Glomerulonephritis.** $\times 320$. 1, Desquamated glomerulus epithelium, arranged in concentric layers, and almost filling capsular space; in the center is the diminished glomerulus; 2, mitosis in epithelial cell.

FIG. 2.—**Chronic Glomerulonephritis.** $\times 320$. The capsule fibrillated, and thick (5); septa extend inward between the desquamated epithelial cells (3) and leukocytes (4); 2, innermost layer of connective tissue surrounding the greatly diminished tuft (1), which is covered with epithelial cells, the lumen containing leukocytes.

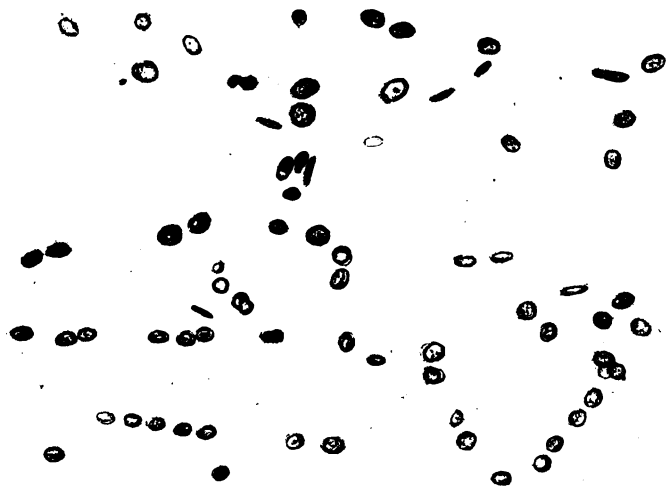


Fig. 1.

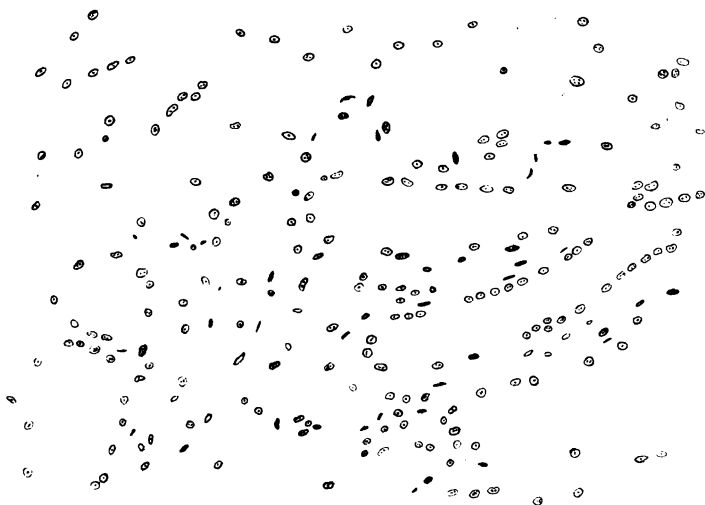
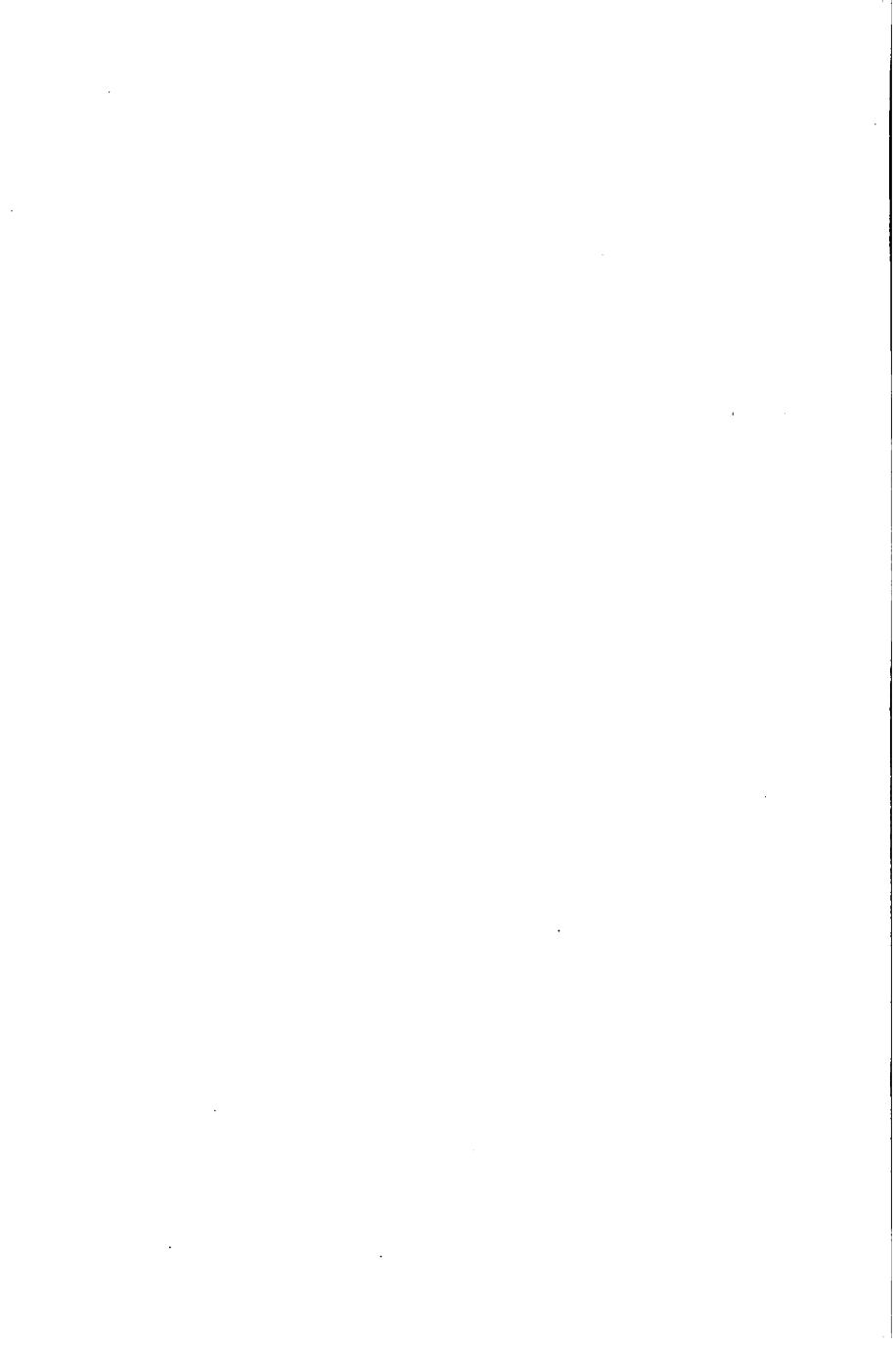


Fig. 2.



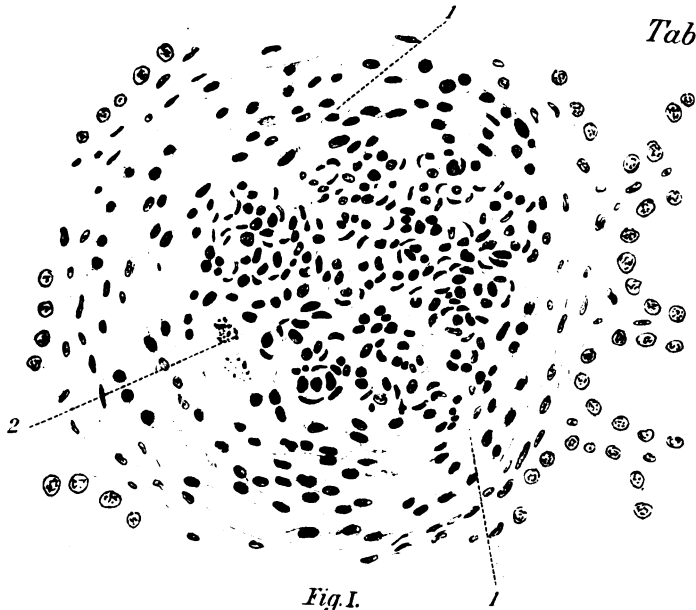


Fig. I.

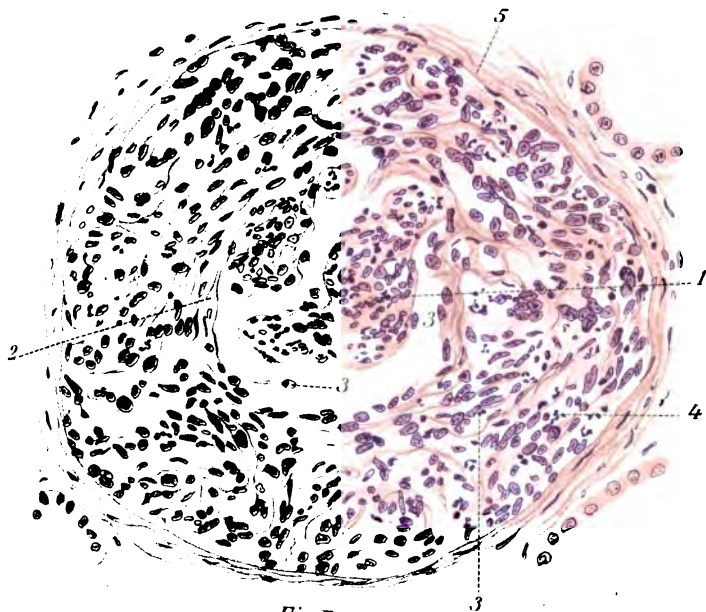
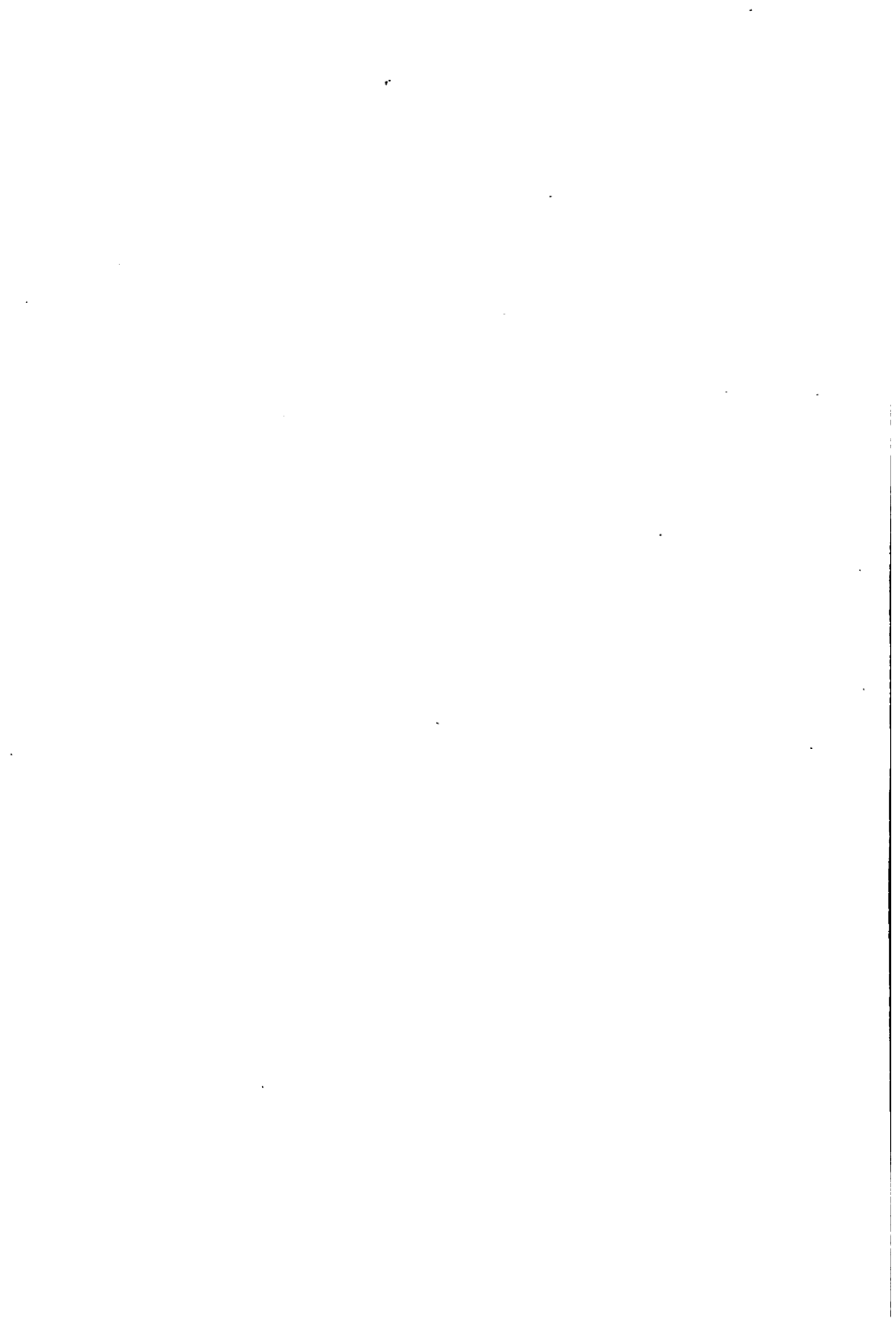


Fig. II.

Lith. Anst. F. Reichhold, München.



remains comparatively smooth as long as there is no loss of parenchyma from degeneration and obliteration of urinary tubules.

At this stage, however (second stage of Bright's disease), the degeneration of the epithelium often becomes irremediable, and thus leads rapidly to more extensive destructions. The flattened cells undergo fatty changes and present in stained preparations a spongy or frothy structure. In many places the nuclei disintegrate, usually after preliminary condensation and clumping of the chromatin. Shed flakes and coagulated albuminous masses fill the widened lumen, and in many parts sections of the tubules may show no cellular structures whatsoever. The basement membrane of the tubules also appears to undergo a process of resolution, and the thickened, fibrous interstitial tissue borders directly on the lumen. By condensation the albuminous masses form homogeneous hyaline cylinders, upon the surface of which may lie occasional epithelial cells (Plate 85, Figs. 1 and 2).

Eventually the altered tubules collapse and are replaced by the surrounding connective tissue, which becomes less cellular, poorer in nuclei, but richer in fibers, and at times it assumes a hyaline appearance (secondarily contracted kidney). If the process is diffuse and uniform, the surface may remain comparatively smooth after contraction of the connective tissue replacing the losses in the parenchyma; but if the process is irregularly distributed, some parts of the parenchyma being spared, then the intact portions project from the surface as granules, while the collapsed portions appear depressed (Plate 87, Fig. 1).

All forms of chronic nephritis associated with extensive productive interstitial changes, whether primary or secondary, are accompanied with characteristic glomerular changes. The capsule is thicker than normal, and in place of the homogeneous basement membrane appears a concentrically fibrillated tissue, at first rather loose in texture, the cells being long, spindle-shaped, and the nuclei nar-

PLATE 87.

FIG. 1.—**Focal Interstitial Nephritis.** $\times 70$. 1, Persistent tubules; 2, area of contraction with broadened, and in many places infiltrated, interstitial tissue; 3, shrunken fibrous glomeruli.

FIG. 2.—**Secondary Contraction of So-called Chronic Parenchymatous Nephritis.** $\times 60$. In the lower part the tubules have a very low epithelial lining and the lumens appear dilated. In the upper part the parenchyma is absent, the interstitial tissue cellular, the glomeruli replaced by fibrous globules, the vessels injected.

row, rod-like, pointed at the ends (Plate 86, Fig. 2). The fibers are separated by small spaces, which it is plain are filled with fluid during life. Tangential sections through a capsule so changed give us the picture of a piece of loose, myxomatous tissue. The cells originate from the pericapsular tissue, which normally is very fine and sparse, and the basement membrane of the glomerular capsules undergoes resolution early in the process. Gradually this fibrous tissue becomes more dense and stiff, the cells change into short spindles, the nuclei stain deeply, the fibrillæ elongate and come closely together. At this stage otherwise almost normal glomeruli are surrounded by thick capsules of connective tissue. The epithelium lining Bowman's capsule may persist, and it is placed directly upon the innermost layer of connective tissue. Usually there is desquamation of the capsular epithelium and of the epithelium covering the capillary loops; the loose cells accumulate in the capsular space, and in fresh preparations fatty changes are demonstrable in the bodies of the cells, just as is the case in acute glomerulonephritis. The increased fibrous tissue in the capsules after a time sends radiating prolongations or septa into the interior of the Malpighian bodies. Between the desquamated cells pass fine connective-tissue sprouts, which at the peripheral parts and upon the inner surface of the capsule unite to form alveolar spaces, inclosing shed epithelial cells, and thus often appearing as if lined with epithelium.

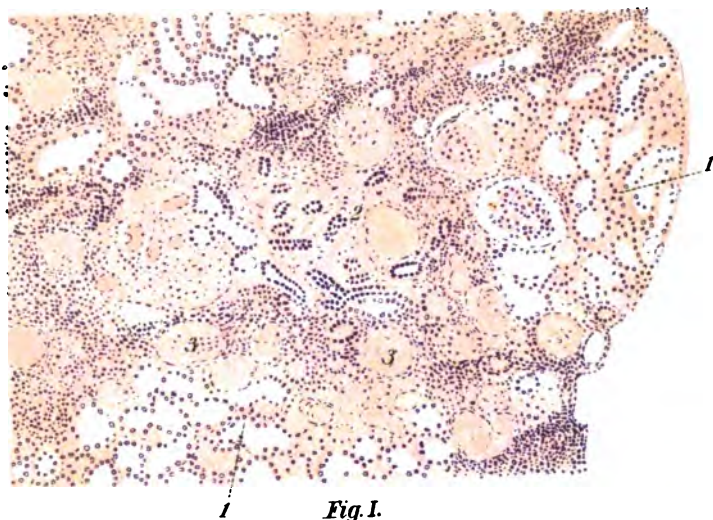


Fig. I.

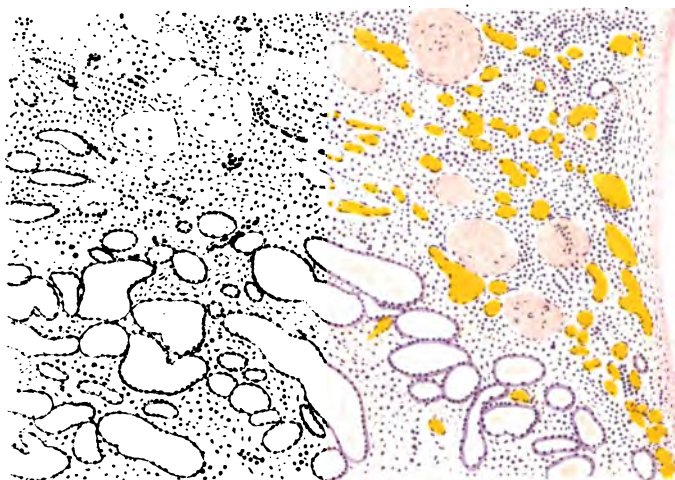


Fig. II.

The capsular space becomes subdivided into several distinct spaces with connective-tissue walls. The innermost space is occupied by the atrophic glomerulus, which remains connected with the capsule at one point corresponding to the exit and entrance of its vessels. This stem, in its turn, may become the starting-point of connective-tissue proliferation, and it is often found surrounded with leukocytes and fibroblasts. The fibroblasts follow the stem into the capsular space, where they spread themselves out upon the remaining vascular loops and join the newly formed bands, thus augmenting the new tissue in the glomerulus. When desquamation is absent, the new tissue from the stem may be the principal cause in the obliteration of the glomerulus, the penetration of the capsule by the surrounding tissue being of but little import. In suitable sections the vascular loops are found covered by a mantle of thick fibrous tissue, which seems to have folded itself over the capillaries. Thus the capsular space is reduced more and more, the capillaries are compressed and undergo atrophy, and sometimes a whole glomerulus contains but one remaining loop. But external compression is not of necessity the only cause of atrophy of the glomerular capillaries; for there is seen occasionally a highly shrunken glomerulus, from which single loops project finger-like into the capsular space, which appears dilated, and generally contains fluid. Here the atrophy is caused from pressure by new tissue upon the vessels at the hilus of the glomerulus. Hyaline thrombosis and epithelial desquamation eventually close the remaining capillary loops, and the glomerulus is definitively obliterated (Plate 86, Fig. 2). The desquamated cells undergo fatty and other retrogressive changes, which transform it into a detritus which, with time, is wholly absorbed. The fibroblasts secrete thicker and thicker fibers, which lie closely, and amalgamate into a hyaline material not unlike the groundwork of cartilage, and the glomerulus is changed finally into a poorly cellular, glistening globule of fibrous

PLATE 88.

FIG. 1.—**Genuine Contracted Kidney.** $\times 65$. 1, Area with normal tubules, above and below which the parenchyma has disappeared almost wholly. The interstitial tissue infiltrated with cells. The glomeruli fibrous and shrunken, closely approximated. In lower left corner artery with thick walls.

FIG. 2.—**Chronic Interstitial Nephritis with Cysts.** $\times 75$. 1, Persistent tubules; 2, cystic tubules, the epithelium lost; 3, colloid contents of cysts; 4, area of contraction with greatly compressed tubules.

tissue. Hyaline change of the newly formed fibrous tissue seems to be quite constant, but, of course, it has nothing to do with the hyaline thrombosis of the capillaries. Later, calcification frequently occurs in the form of small sand-like grains, seen sometimes even with the naked eye upon the exterior and on the cut surface of greatly atrophied kidneys.

Genuine Contracted Kidney.

Genuine contracted kidney, or chronic interstitial nephritis, is a form of slow chronic renal inflammation which in its final result, and especially in its histologic aspects, does not necessarily differ materially from the secondarily contracted kidney in which the parenchyma has been destroyed thoroughly. But the development of this form is characterized from the beginning by marked production of new tissue between the tubules, and degenerative changes in the parenchyma are usually at no time very prominent. In the early stages the kidney is not much diminished in size, but later the continuous substitution of parenchyma by contracting connective tissue leads to progressive diminution of the organ. The unequal distribution of the process leads to the formation of areas in which the changes are further advanced than elsewhere, so that the surface becomes granular; the granulation being finer and more uniform, the more extensive and the farther

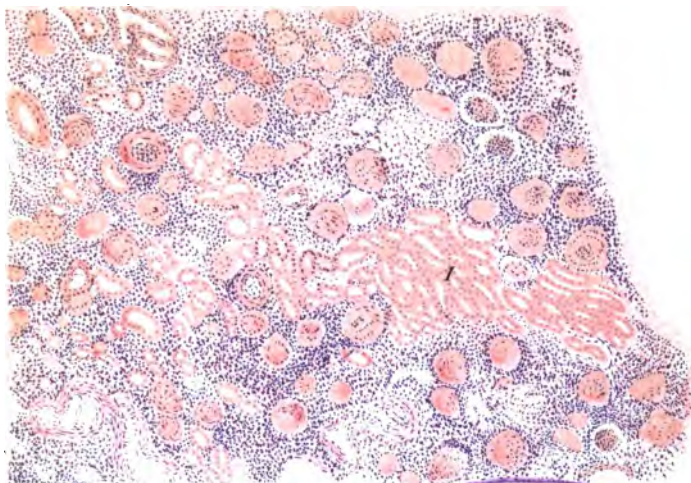


Fig. I.

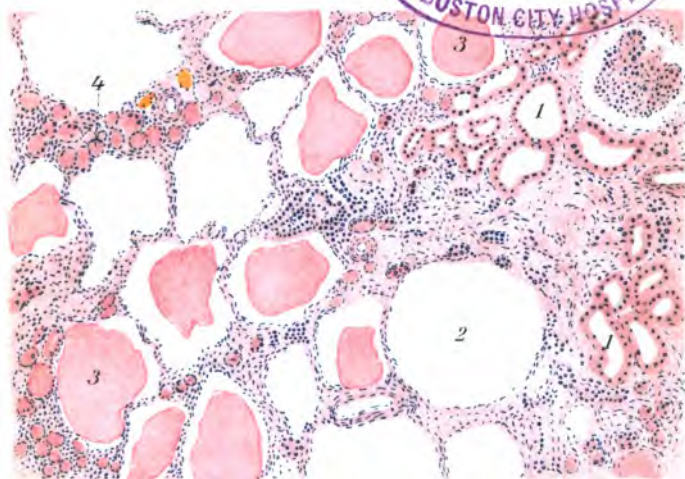


Fig. II.

advanced the shrinking. In such cases the volume is greatly reduced,—sometimes it is only one-third that of the normal,—the consistence is increased, and the amount of blood is very small because of the simultaneous contraction of the vessels; hence the kidney is pale. On the cut surface the shrinkage of the cortex is very striking; sometimes it is reduced to a minimum, the medullary pyramids are shortened and blunted, the bases being broad, the pelvis is often somewhat dilated, and fatty tissue of the hilus and of the capsule is increased.

Microscopically the enormous increase of connective tissue between the tubules dominates the picture. Connective tissue in all stages of development is present, from the cellular fibroblastic stage to the cicatricial and hyaline. In places are found accumulations of round cells, especially in the neighborhood of the vessels (the stellate veins and arteriolæ rectæ). In advanced cases the parenchyma is greatly reduced; the urinary tubules are surrounded and compressed by the concentric fibrous tissue; the lumens narrow, often completely occluded; and at the same time the epithelium is lower than normal. In places the parenchyma is entirely absent, or one finds here and there in the spaces of the connective tissue still a few very narrow tubules or only a few loose epithelial cells. The perivascular tissue is also increased everywhere. All arteries show marked adventitial thickening, and the intima is often the seat of proliferation with narrowing of the lumen: *i. e.*, typical endarteritis, without the necessary existence of arteriosclerosis elsewhere in the body. In the cortex there may be areas in which the urinary tubules have disappeared wholly without leaving any trace, but the remnants of the glomeruli in the atrophic districts always assume the form of fibrous or hyaline balls, which may lie very close together, so that a field normally containing but three or four glomeruli now may contain six to ten times as many remnants. This appearance is explainable by the substitution of the intervening labyrinths by con-

PLATE 89.

FIG. 1.—**Arteriosclerotic Atrophy of Kidney.** $\times 80$. 1, Persisting urinary tubules with low and partly desquamated epithelium; 2, fibrous, shrunken glomeruli; 3, arteries with thick walls; 4, area of contraction in which the tubules are almost wholly replaced by fibrous tissue.

FIG. 2.—**Embolitic Abscess of Kidney in Septicopyemia.** 1, Glomerulus the capillaries of which contain coccal emboli; 2, purulently infiltrated renal tissue; 3, masses of staphylococci.

tracted fibrous tissue, and also, in a measure, by the considerable diminution in the size of the glomeruli themselves. The hyaline globules often are surrounded by concentrically fibrillated fibrous masses. The projections on the exterior correspond in the microscopic section to remnants of renal tissue which has remained more or less normal. The limits between the shrunken and normal tissue are often quite sharp, so that the superficial depressions often form sharp angles at the junction with the healthy parts.

In the advanced cases the medullary substance is also involved, the urinary canals narrowed, in places wholly destroyed, the interstitial tissue increased and fibrous. In the medulla the new connective tissue has an especial tendency to become homogeneous and hyaline.

The surface and the remains of the cortex of contracted kidneys very frequently contain multiple cystic spaces, which contain either an albuminous fluid, hyaline masses, or even globular colloid clumps. Frequently these cysts reach considerable size, projecting singly from the surface, and containing a dark fluid or brownish, smeary, glue-like masses. Their genesis is easily traced by means of microscopic sections: they develop from dilated segments of single urinary tubules, and, frequently, from dilatation of the capsular space of a glomerulus. The latter cysts occasionally contain remnants of capillary loops, and smaller cysts may be found lined throughout with a low, flat epithelium. In the larger cysts there is usually no epithelial

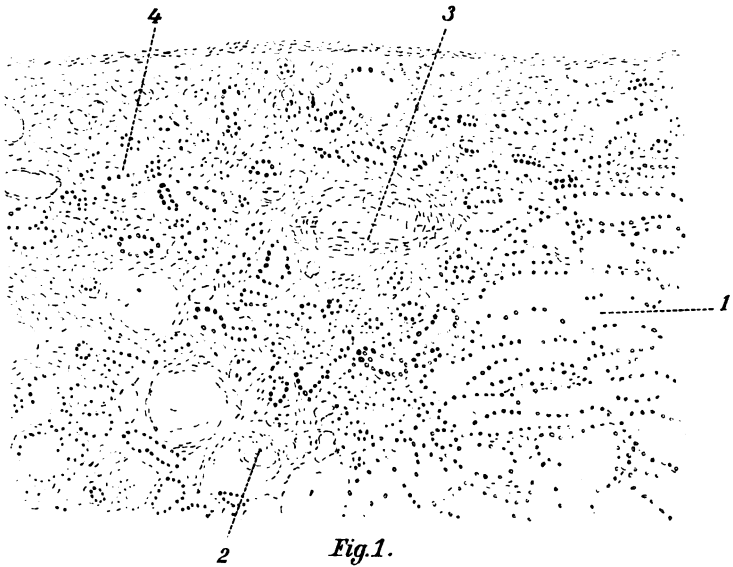


Fig. 1.

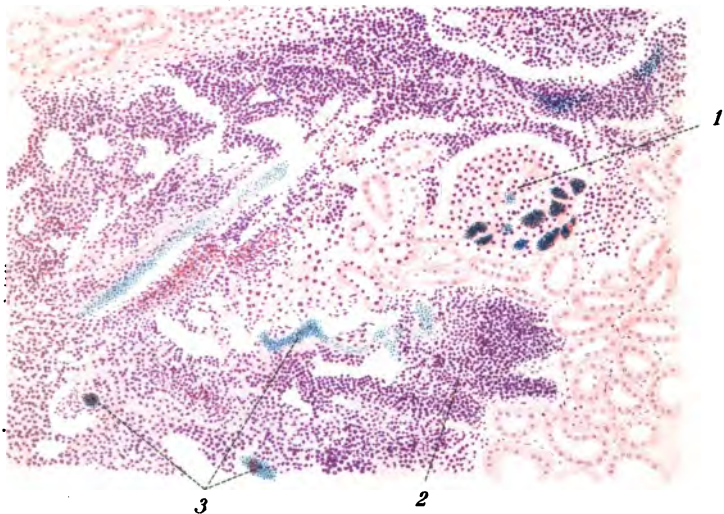
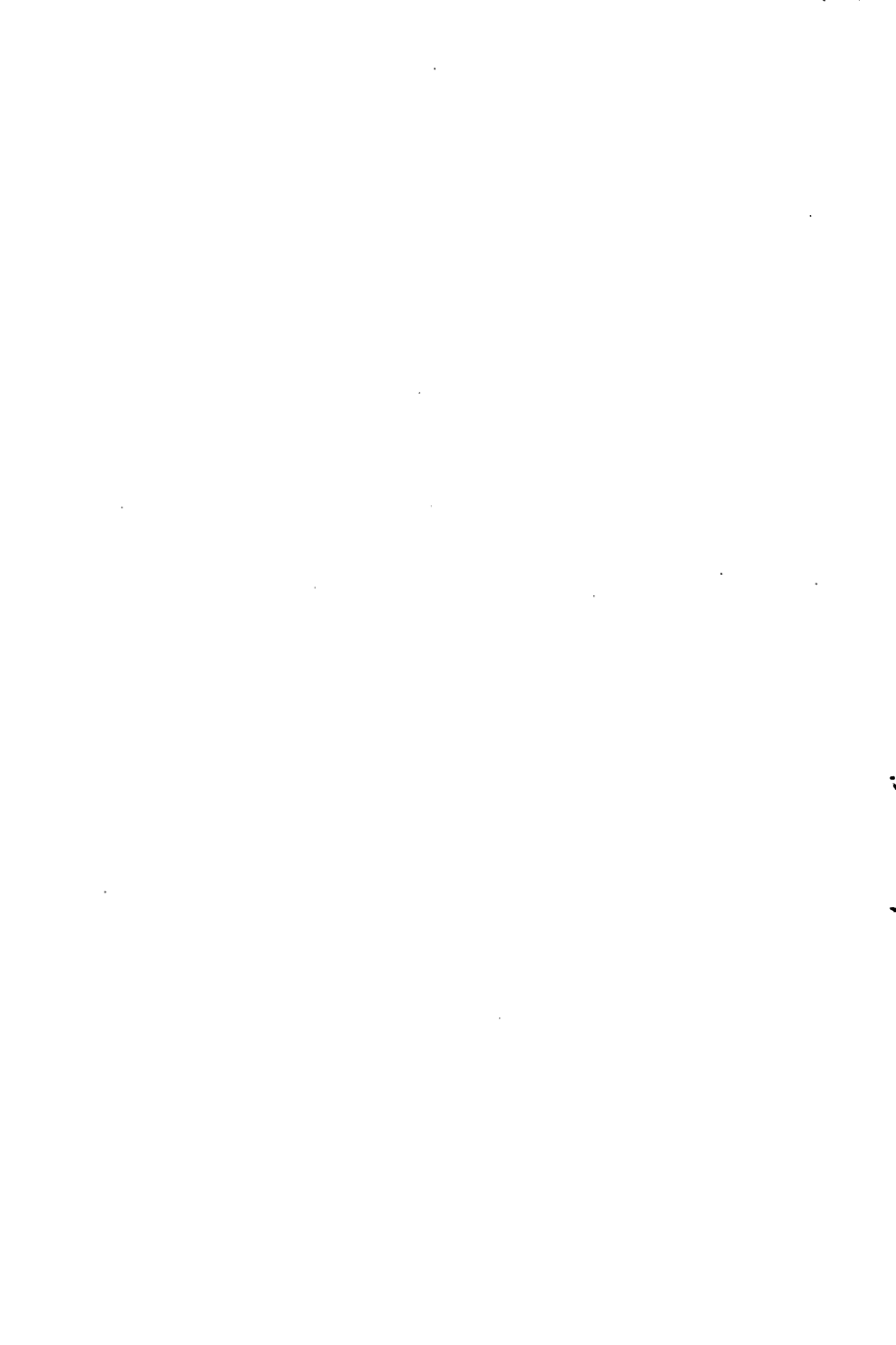


Fig. 2.



lining of the fibrous wall. The colloid masses, which very probably are formed by inspissation of the fluid, may show a concentric microscopic structure, or they are homogeneous flakes with the same tinctorial qualities as the colloid of thyroid gland, and, like this, they often show scalloped margins.

Arteriosclerotic atrophy of the kidney shows no essential difference from the genuine contracted kidney except the striking microscopic changes in the vessels, which may be followed into the smallest arteries (Vol. I, pp. 34-40) (Plate 89, Fig. 1). The so-called lead kidney of chronic lead-poisoning also appears microscopically as a chronic interstitial nephritis and advanced obliterating endarteritis.

Hydronephrosis.

Hydronephrosis also results in contracted kidney, but in this case the atrophy of renal parenchyma is caused by the pressure of the dilated pelvis. Both medulla and cortex are narrowed, the pressure and consequent atrophy first affecting the medullary pyramids, which in consequence become blunted and shortened. When prolonged, the pressure and the obstruction to straight tubules act on the cortex, causing contraction here also.

The microscopic changes are most pronounced in the medullary substance. Connective tissue, usually of hyaline appearance, has developed between the compressed collecting tubules, which themselves often show a peculiar glassy structure.

Higher in the tubules in the cortex the compression leads to partial dilatations with cyst formation. As the albuminous fluid in the cysts becomes thickened, colloid masses result similar to those seen in the ordinary contracted kidney. In the form of renal atrophy now under consideration the glomeruli remain intact the longest. They are surrounded by dense, concentrically fibrillated capsules, and appear to be closer together than usual on

PLATE 90.

FIG. 1.—**Ascending, Suppurative Pyelonephritis.** $\times 80$.
1, Compressed collecting tubules; 2, greatly dilated collecting tubules filled with leukocytes and deeply stained bacterial masses. The epithelium is presented, but very low.

FIG. 2.—**Staphylococci in a Glomerulus in Pyemia.** $\times 520$.
In the capillary loops of the glomerulus lie large heaps of staphylococci; scattered cocci in Bowman's capsule.

account of the shrinking of the intervening tissue. [In advanced cases of hydronephrosis the kidney may be so flattened out and atrophied that it is difficult to recognize it upon the walls of the sac.]

Pyelonephritis.

Inflammations of the kidney may be the result also of extension of inflammation in the pelvis or in the lower parts of the urinary tract. Such inflammation is usually purulent, and is caused, in the majority of cases, by *Bacterium coli commune*. [For recent study of bacteriology of pyelitis and cystitis see Thos. R. Brown, "Johns Hopkins Hospital Bulletin," 1901, XII, 4.] The pelvis of the kidney may be dilated, as in hydronephrosis, and the effects of pressure just outlined may be combined with acute inflammatory changes. The suppurative and ulcerative processes attack the surfaces of the papillæ and result in a greenish eschar of necrotic tissue, pus corpuscles, and fibrin—the so-called diphtheria [or necrosis] of the papillæ, whence the suppuration extends to the tubules and goes upward. It often crosses the arcus renales as it ascends into the tubules of the medullary rays in the cortex—ascending pyelonephritis. Yellowish lines with hemorrhagic zones may extend from the papillæ of the medulla into the cortex, appearing even on the surface of the latter, and involving perhaps the capsule and the surrounding tissue (perinephritis).

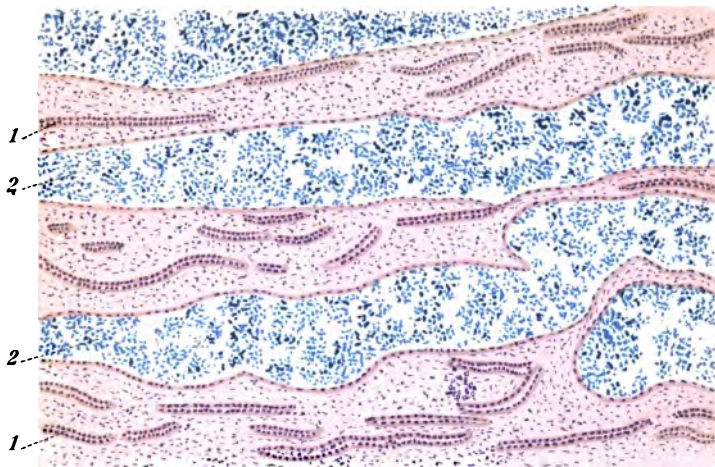


Fig.1.

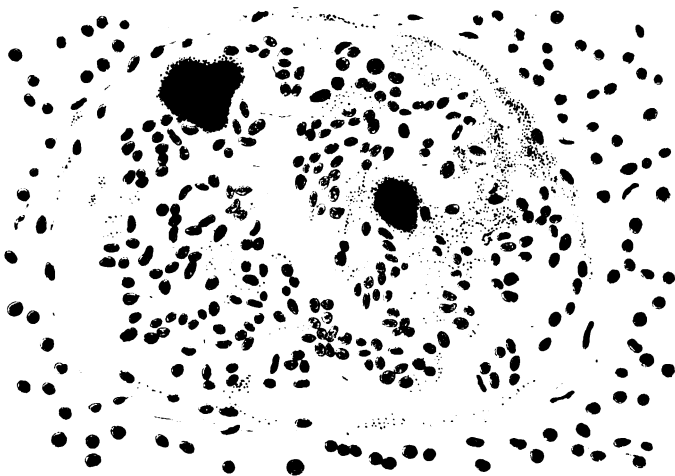


Fig.2.

In the earlier stages, before extensive purulent softening has taken place, the collecting tubules are in part densely filled with leukocytes with fragmented nuclei, and between the leukocytes are cloud-like masses and clumps of bacteria, which often grow to form real tubular casts (Plate 90, Fig. 1). But not all the tubules of the papillæ are involved, for between those greatly dilated are found some not invaded, which appear very narrow and greatly compressed; the intertubular tissue is usually edematous; later, it also is infiltrated with leukocytes. When the process has existed for some time, the epithelium of the dilated tubules is desquamated, leukocytes accumulate between the epithelium and the basement membrane, which is destroyed, and the leukocytic infiltration and purulent softening of the surrounding tissue result. The necrosis produced by the bacteria and their products may lead to confluence of the linear foci into larger cylindrical abscesses. Whole papillæ may be exfoliated. In the cortex also the suppuration extends from the medullary rays out upon the surrounding tissue; the corresponding glomeruli may be filled with pus corpuscles.

Tuberculosis of the Kidney.

Renal tuberculosis may appear in three forms:

1. As hematogenous, embolic, or miliary tuberculosis.
2. As elimination tuberculosis.
3. As the result of extension of tuberculosis of the pelvis and the calyces (phthisis renalis tuberculosa).

The first form is either part of a general miliary tuberculosis or it results as a localized miliary or disseminated tuberculosis of the kidney from the deposition in the cortex, especially the glomeruli, of tubercle bacilli in the blood. The process is analogous to embolic abscess formation and embolic suppurative nephritis.

During the stage of nodule formation one may find, particularly in fresh cases, a glomerulus or capillary vessel in which the bacilli were arrested, and from which their

PLATE 91.

FIG. 1.—**Kidney in Acute Leukemia.** $\times 80$. Urinary tubules and glomeruli crowded apart by dense, uniform interstitial infiltration with lymphocytes.

FIG. 2.—**Embollic Tuberculosis of the Kidney.** $\times 60$. A row of subcortical tubercles with giant cells, the caseous centers coalescing. Round-cell infiltration in the periphery. Stellate veins injected.

specific action spreads. About this center is built up the tubercle in the formation of which take part not only descendants of fixed connective-tissue cells, and round cells, but also the epithelial cells of the tubules and of the glomeruli, which often are found in active mitosis. Giant cells may be formed by the parenchymatous cells, and the impression is often obtained that giant cells are formed by the coalescence of desquamated tubular epithelium (compare General Part, "Tuberculosis"). If glomeruli are present in the nodule, intracapsular giant cells may occasionally be produced by proliferation of desquamated epithelium. The center of the tubercle early disintegrates, and the caseation spreads the more rapidly, the larger the number of bacilli present at the start, while the number of epithelioid cells usually is in inverse proportion to the number of tubercle bacilli present. Numerous adjacent nodules may coalesce and extensive caseous masses result—the so-called conglomerate tubercle. This occurs mostly in local disseminated renal tuberculosis (Plate 91, Fig. 2).

The second form of tuberculosis, the elimination tuberculosis, occurs in the same manner as the abscess of similar mode of origin. In this case the tubercle bacilli break through the glomeruli and are carried with the urine into the tubules, where they may be arrested on account of some obstruction, most frequently a cast. This happens usually in the straight tubules of the medullary substance. As the bacilli proliferate, the tubercle is formed, not in a blood-vessel, but in [and about] a urinary tubule. The nodules present a more cylindrical form, but are otherwise

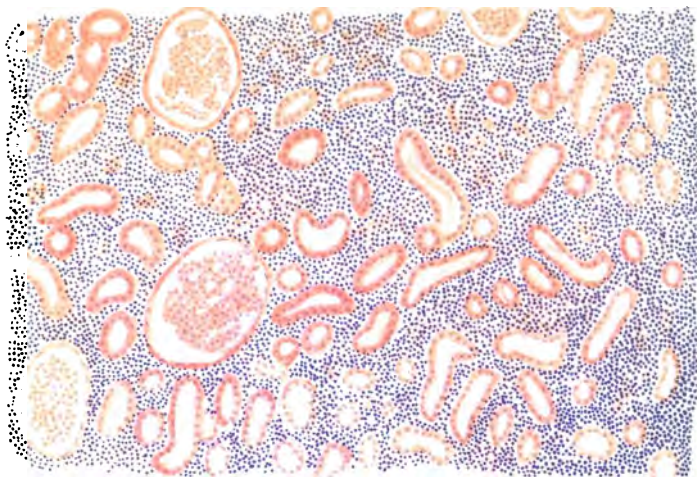


Fig. 1.

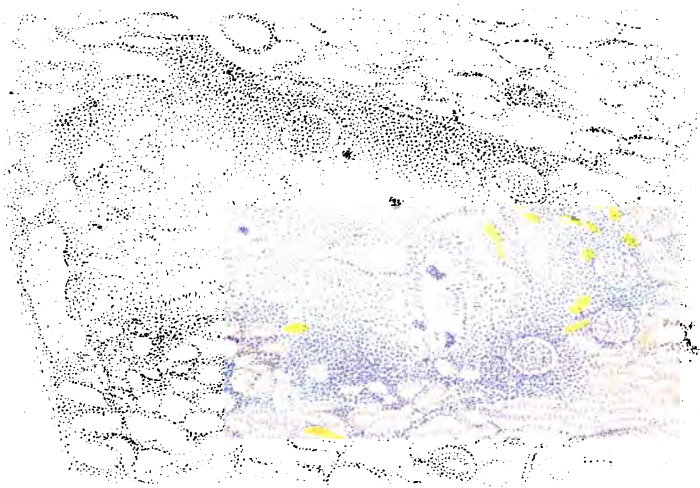


Fig. 2.

similar in structure to the hematogenous. The tubular epithelium partakes in the formation of epithelioid cells. In this form extension takes place mostly in the direction of the long axis of the straight tubules, so that to the very apex of the papillæ may run lines composed of confluent nodules or caseous masses. By the confluence of such stripes entire papillæ may become involved in caseation (nephritis papillaris caseosa).

The third form of renal tuberculosis results from the extension of the disease from the ureters or pelvis. The course is quite similar to that of suppurative pyelonephritis, but complicated by the formation of specific tuberculous nodules. These nodules form first at the apex of the papillæ projecting into the caseous calyces. The bacilli penetrate between the canals, and also into the canals when occlusion removes the expelling force of the urinary streams, and they may extend into the cortex. Thus again originate radiate caseous stripes, as in tuberculosis from elimination, but in the opposite direction. Tuberculosis of the kidney secondary to pelvic tuberculosis is often complicated by the simultaneous entrance of pus microbes, in which case the histologic appearances are mostly those of suppuration.

Syphilis.

Various forms of chronic and degenerative nephritis are regarded clinically as the consequence of general syphilitic infection, even though the anatomic characters are not specific. Contracted kidneys often show radiating scars, which, in conjunction with obliterating endarteritis, point in the direction of syphilitic genesis with considerable probability. Specific luetic productions in the form of gummas are rare in the kidney. In structure they correspond to gummas elsewhere ("Atlas of General Pathologic Histology," "Syphilis"). They are distinguished from conglomerate tubercles by the marked fibrous capsule, which is nearly always constant, and by the obliterating endarteritis in the neighborhood.

PLATE 92.

FIG. 1.—**Tuberculosis of the Adrenal.** $\times 65$. 1, Normal adrenal tissue; 2, coalesced caseous centers; 3, margin of confluent tubercles with round cells.

FIG. 2.—**Diphtheroid Cystitis.** $\times 92$. 1, Persistent epithelium; 2, superficial muscle layer; 3, infiltrated submucosa; 4, prominent eschar of necrotic material, leukocytes, and fibrin.

In congenital syphilis the kidneys often show specific changes in the form of infiltrations about the vessels of the cortex, as well as atrophic and degenerative processes in the tubular and glomerular epithelium (von Hecker), leading not infrequently to shrinking of one or both kidneys. In such cases the vessels show advanced obliterative changes.

Leukemia.

Leukemia appears in the kidney in the form of circumscribed lymphomas or as diffuse leukemic infiltrations. In the beginning the vessels, by virtue of the increased number of white cells, appear in the sections as especially rich in nuclei on account of the accumulation of numerous leukocytes and lymphocytes. Later the interstitial tissue is infiltrated with cells, and hence it is rich in nuclei and apparently wider than normal, the tubules and glomeruli being pressed apart (Plate 91, Fig. 1). Macroscopically the kidney in this stage is large, dry, and very pale. Still later the cells penetrate the basement membrane and infiltrate the tubules and the glomeruli. These structures may be compressed and reduced to complete atrophy. Thus arise focal leukemic infiltrations, within which only occasional remnants of renal tissue are encountered.

Tumors of the Kidney.

Among the typical tumors of the kidney fibromas are especially frequent, usually only as minute nodules in the

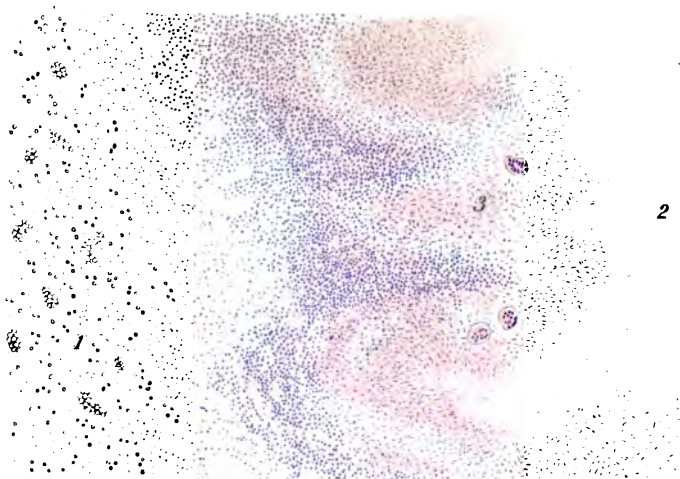


Fig. 1.



Fig. 2.

cortex as well as in the medulla. Occasionally they occur as multiple growths, in which case they are easily mistaken for granulomas on macroscopic examination. Very rarely large fibrous tumors have been observed in the kidney.

Small lipomas are also comparatively frequent in the kidney. They are usually situated in the outer layers of the cortex, and consist of typical fat cells. The adjacent tubules appear pushed to the side somewhat.

Sarcomas of the kidney are seen especially in children, occasionally as congenital growths. They were formerly often regarded as carcinomas. It mostly concerns sarcomas with small round cells, between which remnants of tubules may be observed. The tumors often reach the size of a man's hand and even more, and are soft and cellular. They have been observed frequently to contain glycogen. Occasionally they are combinations of sarcoma with myoma, with smooth as well as with striated muscle-fibers—leiomyosarcoma and rhabdomyosarcoma. [Concerning the embryonal adenosarcoma of the kidney, a tumor in which embryonal tubules are scattered throughout the purely sarcomatous or sarcomyomatous tissue, see "Progressive Medicine," 1900, March, where the literature is cited.]

The most common epithelial tumor of the kidney is derived from misplaced remnants of adrenal tissue, as first correctly recognized by Grawitz, having been regarded previously as lipoma or as carcinoma. On account of their genesis these tumors are often called hypernephromas (*struma lipomatodes renis aberrata*). They vary in size from minute nodules to large masses, and at times they give rise to multiple metastases in various parts of the body. The microscopic structure in general is of an adenomatous type, and is made of very large epithelial cells with pale vesicular nuclei. The cell bodies generally contain innumerable fat droplets, and seem to be greatly disposed to fatty changes, hence the frequent confusion with lipomas. The stroma is very fine and provided with

delicate vessels in which tears often give rise to large hemorrhages.

Adenoma and carcinoma also occur in the kidney as primary tumors.

THE URINARY BLADDER.

The most common lesion of the urinary bladder is inflammatory changes produced by the entrance of microbes by way of the urethra. The mucous membrane is diffusely swollen, reddened in spots, especially in the vicinity of the trigonum. The urine in the bladder is generally turbid, particularly in the lower layers.

Simple catarrhal cystitis is characterized microscopically by increased epithelial desquamation and by leukocytic infiltration of the mucosa. Leukocytes are often found in large numbers on their way outward between the epithelial cells. The submucosa shows follicular masses of round cells, the vessels being greatly dilated and filled with red blood cells.

Certain chemical agents, long-continued accumulation of urine in the bladder on account of obstruction to the outflow, as in stricture of the urethra, as well as the formation of concrements in the bladder, may give rise to necrotizing inflammations of the vesical mucosa, often designated as diphtheritic cystitis, or, preferably, diphtheroid cystitis. Larger or smaller eschars form in the mucosa as dark red, or later grayish-red, swollen areas, the surface of which is often sprinkled with sand-like concretions formed by precipitation of triple phosphates. Microscopic sections (Plate 92, Fig. 2) usually show a fairly sharp line of demarcation between the more nearly normal mucous membrane and the necrotic areas. The necrosis involves the mucosa, generally also the muscularis mucosæ and parts of the submucosa; the nuclei are no longer visible; enormous accumulations of leukocytes form, traversed by rather thick networks of fibrin. The deeper layers of the sub-

mucosa, and even the muscularis, may be infiltrated with leukocytes. At times the eschar is deep red from the presence of blood due to erosion of the superficial vessels. Continued leukocytic infiltration about the margins of the eschar is eventually followed by exfoliation of the necrotic area and the formation of an ulcerating surface.

The mucous membrane of the bladder not rarely is the seat of tuberculosis in general miliary tuberculosis, and also more frequently in localized tuberculosis of the urinary tract. In the first instance multiple minute nodules form in the subepithelial tissue. After some time the central caseation may extend to the surface, and, on breaking through, give rise to "lenticular" ulcers. In general urogenital tuberculosis there are usually larger tuberculous ulcers with caseous floors, in which the continued development of nodules carries the process deeper and deeper. Even the muscularis of the vesical wall may be invaded by tubercles.

In leukemia there are also frequently typical alterations in the bladder, in the form of at times quite extensive infiltrations in the mucous membrane, which in places may crowd out the epithelium completely. The stratum proprium of the mucosa is densely infiltrated with leukocytes extending out among the epithelial cells, which are pushed apart so that lymphomatous masses project free upon the inner surface.

The most frequent tumor in the bladder is papillary fibroma, which originates in a proliferation of the fibrous tissue in the stratum proprium. The epithelium is lifted and the branching growth of the fibrous tissue becomes covered by glove-like inclosures of epithelial lining. In this manner the tumors acquire a complicated, delicately branching structure. The stroma carries numerous thin-walled vessels, which when torn may lead to extensive, even dangerous, hemorrhages.

Pieces from the surface of these villous tumors of the bladder may appear in the urine, where their recognition

may establish the diagnosis. Fragments of this sort usually are covered no longer with intact epithelium, as this is partially shed and incrustated with lime salts. Wherever intact, the epithelium shows many layers of cells, as in the normal vesical wall.

Sometimes the papillary fibroma, originally a benign tumor, may develop into carcinoma by proliferation of its epithelium downward into the muscularis.

THE URETHRA.

The male urethra is examined anatomically with relative infrequency. One of the commonest changes in the male urethra is acute catarrhal inflammation, caused by the invasion of the mucosa by the specific agent of gonorrhea.

Acute gonorrheal urethritis is characterized microscopically by a severe mucopurulent inflammatory process. The appearances vary in degree in different parts of the urethra. While the anterior portion, the fossa navicularis, which is lined with stratified epithelium, offers considerable resistance to the invasion of gonococci, they more easily penetrate between the cylindrical cells of the posterior parts. In consequence, active desquamation of the cells takes place, which affects also the cells of the deeper layers. The cells appear separated from their connections, the uppermost are clouded, the nuclei in part often absent, and the protoplasm commonly contains heaps of typical gonococci in pairs. Gonococci are found throughout all parts of the mucosa, even in the stratum proprium, always surrounded by accumulations of leukocytes, which migrate in large numbers through the epithelial lining. Littre's glands are commonly the seat of the largest accumulations of organisms, because here they are not so easily washed away by the stream of urine.

The lumen of the glands is often filled with desquamated epithelium and with leukocytes, both containing gonococci in large numbers.

Oftener still are found in cadavers the chronic inflammatory processes that develop in the course of gonorrheal urethritis. The urethral mucosa then appears thickened and hard in places; underneath may be felt nodular masses, and occasionally there are circular constrictions of the lumen of the urethra, especially in the membranous part. In advanced cases the strictures may lead to almost complete closure of the urethra. Microscopically such cases show pronounced alterations in the deeper layers of the mucosa in the form of cicatricial fibrous productions often reaching into the corpus cavernosum. In place of the loosely arranged fibrous tissue, rich in elastic elements, appear sharply circumscribed layers of densely fibrillated tissue, poor in cells, the elastic fibers being almost all destroyed. In the vicinity of the scars are still occasional heaps of round cells. But the epithelial covering usually also manifests changes. Over extensive scars it often appears flattened, smooth, atrophic, the cell layers being diminished, the single cells flattened. Occasionally there is found a peculiar metaplasia of the epithelium with partial hornification. The fibrous and broadened stratum proprium is raised into papillæ, which lift the epithelium above the level of the adjacent mucosa. The superficial cylindrical epithelium of the pendulous part is replaced by large flat cells, similar to the cells of the rete Malpighii; the upper layers contain fine deposits of granules and clumps of keratohyalin, and pass into thin horny plates, which cover the lining as a real stratum corneum. This process is designated keratosis urethræ, and is often sharply circumscribed. To the naked eye the areas appear as circumscribed white flecks, which at first sight may be mistaken for membranous deposits; but, of course, they cannot be stripped from the underlying tissue.

Among tumors of the male as well as the female urethra may be mentioned papillary fibromas, which occur in the vicinity of the external orifice in consequence of continued irritation such as may be caused by gonorrheal

infection. They are usually called acuminate condylomas, and consist of branching papillæ of vascular stroma, clothed on the surface with stratified epithelium, in which the prickle cells of the rete usually are well marked. Often leukocytes are seen between the epithelial cells.

THE ADRENALS.

The adrenals consist of a fibrous capsule, which sends trabeculæ into the interior of the organ, and of parenchyma. The parenchyma is composed of the yellowish cortical substance and of the darker colored medulla. The cortex consists of three zones: the external, of rounded cell masses—the so-called zona glomerulosa; a broader middle zone, in which the cells are arranged in long, parallel columns—the zona fascicularis; and an inner narrower zone, in which the cells form smaller masses in an irregular fibrous network—the zona reticularis. The cells themselves are large, rounded, and protoplasmic, the nuclei not very dense.

The medulla is characterized by the presence of pigment. It is formed of finely granular, polygonal cells, which are assumed to belong to the sympathetic nervous system [by some]. The cells are arranged in round or cylindrical, interlacing masses. The medulla contains a dense network of nerves derived from the celiac plexus.

The most frequent lesion in the adrenal, found at post-mortems, is tuberculosis. It may be associated with the intense brown discoloration of the skin that forms part of the symptom-complex of Addison's disease. Tuberculosis occurs either in the form of small circumscribed nodules, as in general miliary tuberculosis, and even more frequently in conglomerate masses with marked tendency to caseation (Plate 92, Fig. 1). The tubercles commonly start in the inner layers of the cortex, whence the process spreads into cortex and medulla. In the earlier stages the parenchymatous cells may be seen to take part in the formation of epithelioid cells. The conglomerate tuberculous masses do not present any changes of special histologic interest.

Syphilis, especially the congenital form, may cause characteristic changes in the adrenal. In the luetic newborn the cortico-medullary junction may contain circumscribed

miliary nodules with caseous centers, and there may be newly formed fibrous tissue as well as small masses of epithelioid cells between the columns of the zona fascicularis (Oberndorfer).

[The adrenal may be the seat of extensive amyloid degeneration, which seems to first involve the cortex. In the medulla chronic interstitial changes may crowd out the parenchymatous elements. Addison's disease may be associated with both these changes, when extensive.]

THE MALE GENITALIA.

The prostate consists of a fibrous stroma in which are smooth muscle-fibers in considerable numbers; but under normal conditions the muscle-fibers run singly, and are not gathered into larger bundles. Scattered about are glands of branching, tubular structure, whose ducts empty into the colliculus seminalis. The gland cells are low cylindrical cells placed directly in a single layer on a basement membrane. The ducts are clothed with many-layered cylindrical epithelium, like the urethra.

The testes are tubular glands inclosed by a very firm fibrous capsule, the tunica albuginea. The inner layer of this tunic is rich in blood-vessels, and is therefore known as the tunica vasculosa. The capsule sends inward connective-tissue septa, which traverse the whole organ and unite into a dense mass of fibrous tissue, the so-called mediastinum testis [or corpus Highmori]. The septa give origin to a fine reticular tissue which surrounds the seminiferous tubules. In addition to collagenous fibers and cells, the stroma contains large protoplasmic cells in varying numbers, the so-called interstitial cells; in adults these cells frequently contain fat, pigment granules, and also crystalline bodies. The seminiferous tubules run between the septa, beginning probably with blind ends and

PLATE 93.

FIG. 1.—**Hypertrophy of the Prostate.** $\times 54$. 1, Remains of prostatic glands; 2, proliferated, broad muscle bundles.

FIG. 2.—**Tuberculosis of the Prostate.** $\times 65$. 1, Dilated glandular tubule; 2, concentrically lamellated prostatic concretions (so-called corpora amyloidea); 3, giant cells; 4, confluent tubercle with radially arranged epithelioid cells.

filling the interseptal spaces with their numerous coils, passing at the apices of the spaces into the tubuli recti, which are collected into the rete testis Halleri. The tubuli contorti consist of an external fibrous wall, a homogeneous basement membrane, and a stratified epithelial layer of complicated structure. Nearest the basement membrane lie the clear cells of Sertoli, next to which lie, in the active organ, the cells that produce spermatozoa, the spermatogenic cells [spermatogonia], which are large cubical elements with frequent mitotic figures. They grow toward the lumen and form the spermatocytes; the latter push their offspring, the spermatids, still nearer the lumen, and from these are derived the spermatozoa or spermatosoma.

The tubuli recti have only a basement membrane and a single layer of cubical epithelium.

The epididymis is formed by the ductuli efferentes, the walls of which are formed by a layer of cubical and cylindrical ciliated cells resting upon a layer of fibrous tissue and smooth muscle-fibers. The vas deferens of the epididymis also has ciliated cylindrical epithelium.

THE PROSTATE.

The dilated glandular tubules and, more frequently, the ducts of the prostate, especially in older persons, under normal conditions may contain concretions of varying size, from the microscopic to granules as large as millet-seed. These concretions show on the cut surface a plainly concentric, lamellated structure. They are rounded, oval,

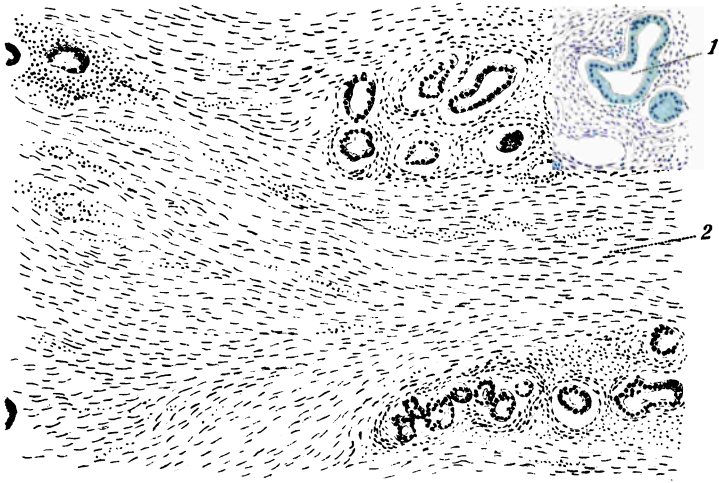


Fig. 1.

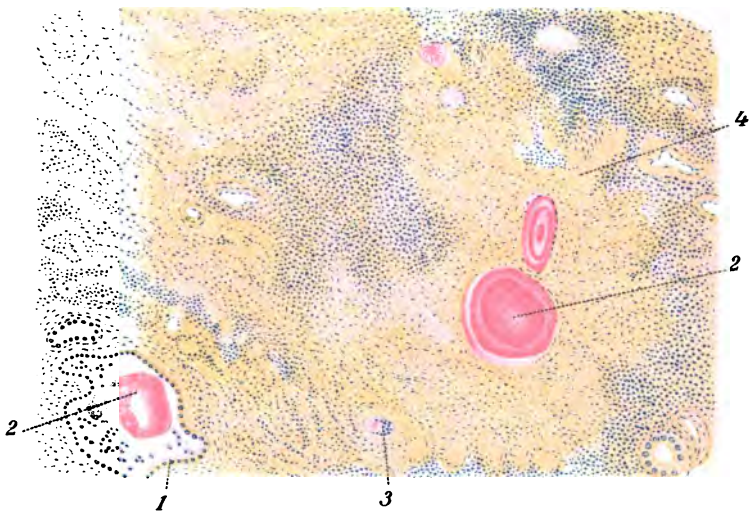
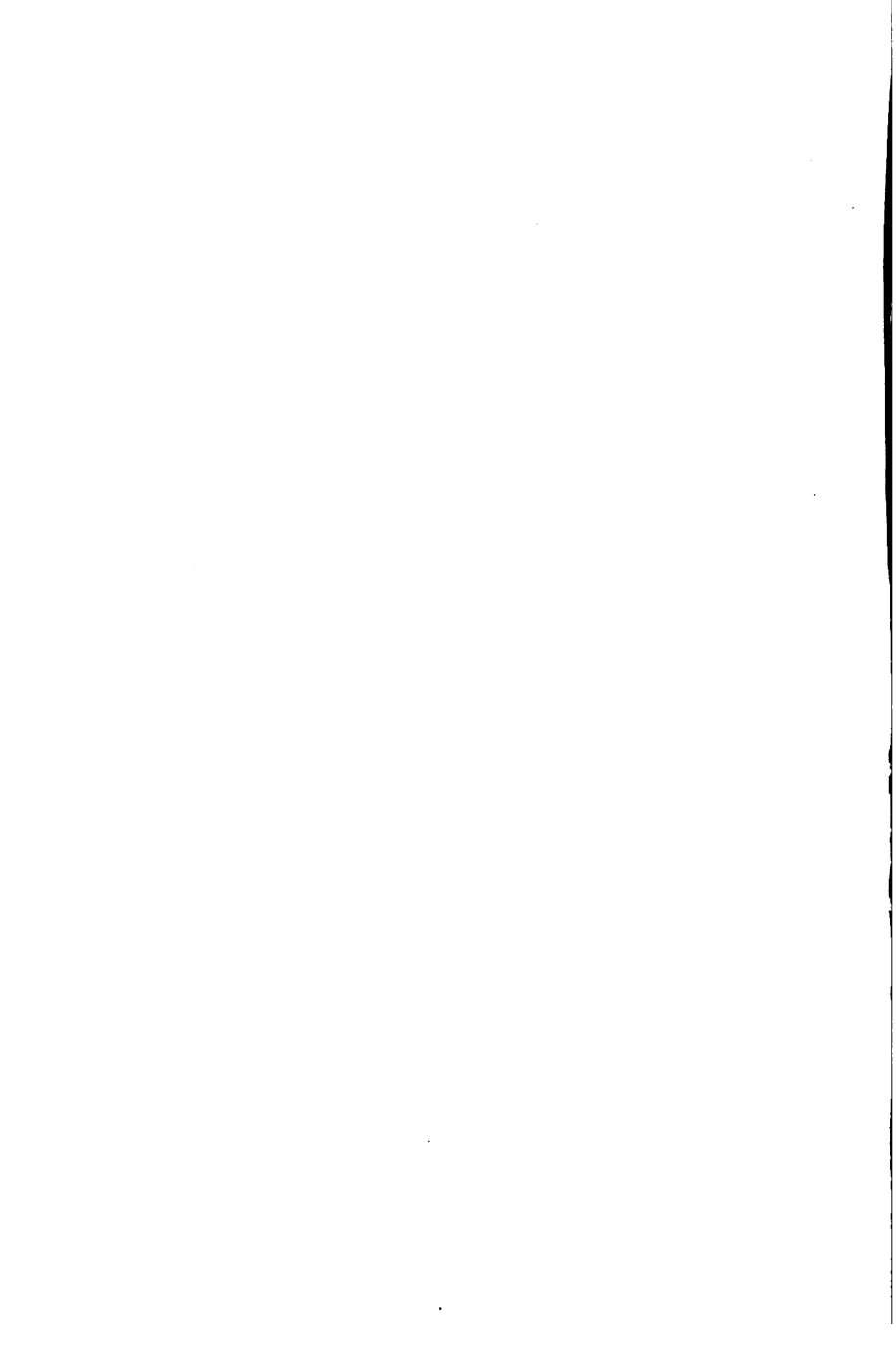


Fig. 2.



or shaped like whetstones, and give a reaction similar to that of amyloid material. (Plate 93, Fig. 1). Sometimes they are present in very large numbers, filling the tubules and glands to distention. Large concretions may occlude the ducts.

Acute inflammations of the prostate frequently develop from gonorrheal urethral infection. The organ becomes larger and more succulent. Macroscopically there is a mucopurulent process of the gland tubules, which are filled with desquamated epithelial cells and leukocytes. Leukocytes may accumulate in the stroma and in the muscular tissue, sometimes to such an extent as to form circumscribed purulent foci. Prostatic abscesses may develop when the infection is very severe or when the glands are prevented from emptying their contents.

With advancing age the prostate often becomes enlarged, thus causing obstruction to the outflow of urine, especially when the so-called middle lobe is affected. The enlargement or hypertrophy may depend upon increase in the glandular substance, the tubules increasing in length and becoming convoluted, or on increase of muscular tissue. The latter is the more frequent. In place of isolated muscle-fibers and bundles there are seen extensive layers of smooth muscle substance, and there may be enlargement of the single muscle-fibers. This proliferation of muscle cells naturally leads to a relative or absolute diminution of glandular substance, so that in many fields one sees only smooth musculature. By concentric arrangement of the muscle-fibers circumscribed myomas are formed, while the glandular elements become less and less marked, the tubules being narrow and compressed (Plate 93, Fig. 1).

In tuberculosis of the genito-urinary organs infection of the prostate often occurs, the nodules frequently developing in the interior of the prostatic glands after entrance of the bacilli by way of their ducts. Large caseous masses may form, involving even an entire lobe.

PLATE 94.

FIG. 1.—Atrophy of Testicle and Proliferation of Interstitial Cells. $\times 80$. 1, Islands of proliferated cells. Stroma broad; tubules largely absent.

FIG. 2.—Senile Atrophy of Epididymis. $\times 80$. Stroma increased; seminal tubules diminished; epithelial cells filled with brownish pigment in the part nearest lumen.

THE TESTICLES.

Inflammations of the testicles occasionally develop in infectious diseases, especially in epidemic parotitis [mumps], in which an acute metastatic orchitis may develop, beginning as a diffuse infiltration of the intertubular tissue and sometimes ending in purulent softening and abscess formation. Leukocytes accumulate in the intertubular tissue, penetrate the basement membranes of the canals, and infiltrate the epithelial lining, the cells of which are desquamated. The lumen is filled with desquamated cells and leukocytes and the seminiferous tubules may be destroyed completely. The abscess may break through externally, and the two layers of the tunica vaginalis may form adhesions. Suppurative processes may spread from the tunica vaginalis to the testicles, as in peritonitis, with patent inguinal canal, when purulent exudate may accumulate in the scrotum. The tunica albuginea becomes loosened in its structure, leukocytes crowd into it between the fibrillæ, and extend into the septa, the stroma, and even the tubules.

Chiari has described a peculiar form of orchitis in variola—orchitis variolosa—characterized by the formation of multiple foci of necrosis in the testes, easily seen macroscopically as yellowish spots up to the size of a pea. Microscopically the centers of these areas contain tubules whose epithelium, having lost its nuclei, lies loose and in flakes in the lumen. Toward the periphery are accumulations of nuclear detritus and densely arranged leukocytes,

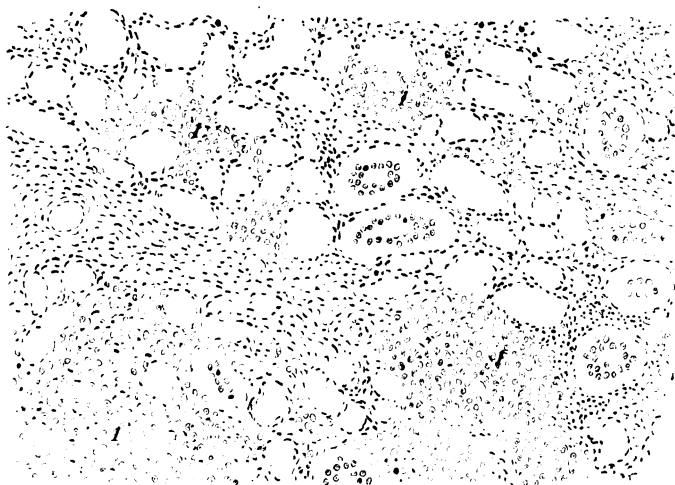


Fig. 1.

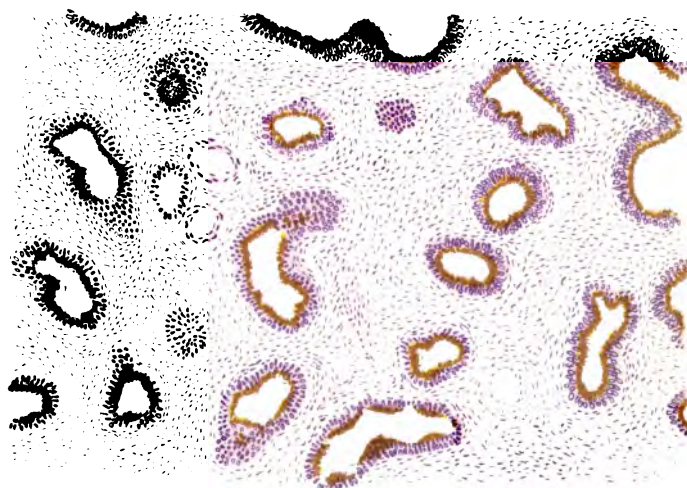
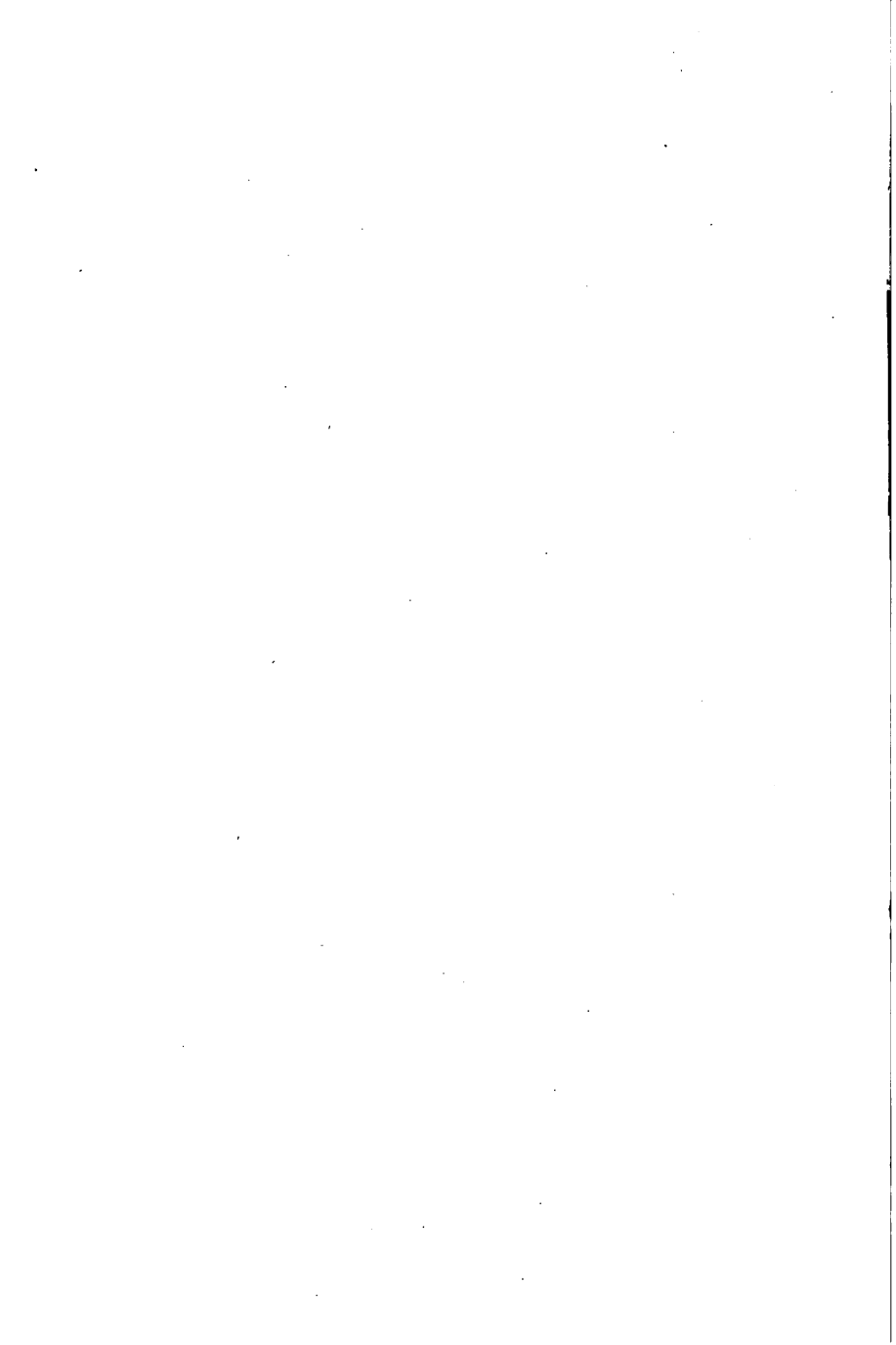


Fig. 2.



but there is no real purulent softening. The intertubular tissue is also necrotic and at the outskirts infiltrated with leukocytes. In rare instances the vessels contain heaps of cocci.

In the epididymis inflammatory processes most commonly develop from extension from urethra and prostate. Abscesses may form, the contents of which may become inspissated and give rise to dry, caseous masses, which are surrounded by fibrillated tissue ("gonorrheal tubercle"). At the same time the interstitial changes may cause compression of the tubules and lead to complete occlusion of the efferent ducts. Many a case of azoospermia owes its existence to chronic inflammation of this kind of the epididymis.

In old age there is often atrophy of the testes, characterized microscopically by increase of interstitial tissue and gradual atrophy of the seminal tubules. Where the basement membrane of the tubules is broken up the connective tissue extends into the lumen, and soon causes the previously atrophic epithelium to disappear completely. Atrophic testes may contain a few tubules whose basement membrane is replaced by thick, concentrically fibrillated layers of connective tissue. The tissue becomes very firm and deeply pigmented, owing to the deposition of brownish pigment granules. The seminal tubules cannot be drawn out from the cut surface (Plate 94, Fig. 1).

Similar atrophic changes occur in the epididymis in old age—increase of interstitial tissue, shrinking and flattening of the epithelium, and deposition in the latter of brownish pigment (Plate 94, Fig. 2).

A peculiar form of testicular atrophy results from proliferation of the interstitial cells normally present in the interstitial tissue as single cells or as small heaps of cells. At times these protoplasmic cells, with their clear nuclei, form larger accumulations; they lose their rounded outline and assume polygonal forms on account of mutual pressure, and the cell masses remind one of the structure of the

PLATE 95.

FIG. 1.—**Tuberculosis of the Testicle.** $\times 65$. 1, Normal tissue ; 2, confluent tubercles with numerous giant cells and occasional remnants of seminal tubules (3).

FIG. 2.—**Gummous Orchitis.** $\times 25$. 1, Compressed, occluded, and atrophied tubules ; 2, fibrous wall of gummous nodule ; 3, artery with marked internal thickening.

liver. They may constitute the larger part of the tissue, the accumulations being mostly stellate in form, the prolongations passing out into the surrounding stroma. In marked instances the seminal tubules may be present only here and there, and yet there may be no appearances of atrophy about them. Occasionally these remarkable proliferations are found even in young individuals. Their genesis and significance are not understood. In pernicious anemia and in general hemochromatosis the proliferated interstitial cells may be filled with pigment granules, as in certain animals (Eber), so that the organ has a dark brownish color. In hibernating animals Hansemann found that the interstitial cells atrophy during hibernation and multiply afterward.

Testis and epididymis are often the seat of infectious granulomas. Tuberculosis is usually primary in the epididymis, involving the testis later by extension, while gumma more commonly is primary in the testis.

Tuberculosis of testis appears in two forms, according to its point of origin. In general miliary tuberculosis, miliary nodules spring up in the interstitial tissue ; they may involve the tubules by further growth. In the far more frequent form caused by extension of an existing genito-urinary tuberculosis the infection takes place by way of the efferent seminal ducts, and the primary seat of the nodules is in the wall of the tubules of the testicle. In the earlier stages the transformation of epithelial cells into tuberculous epithelioid cells may be studied very well (Gaule). The desquamated epithelial cells proliferate

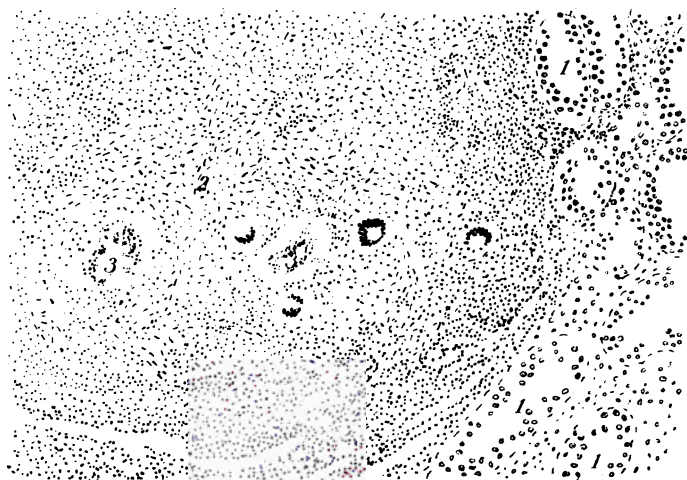


Fig. 1.

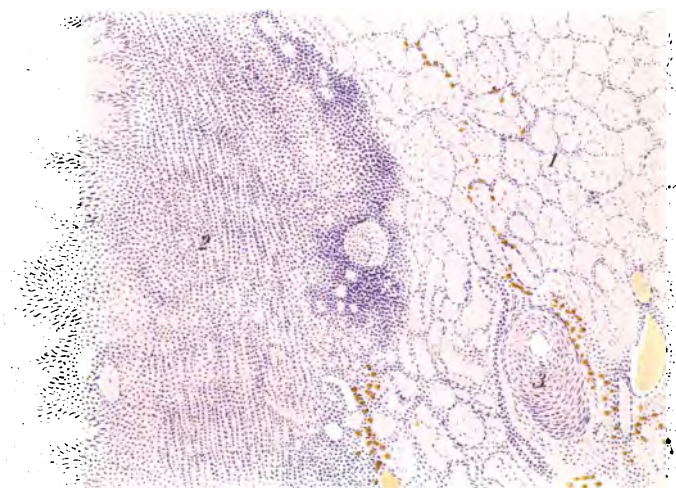
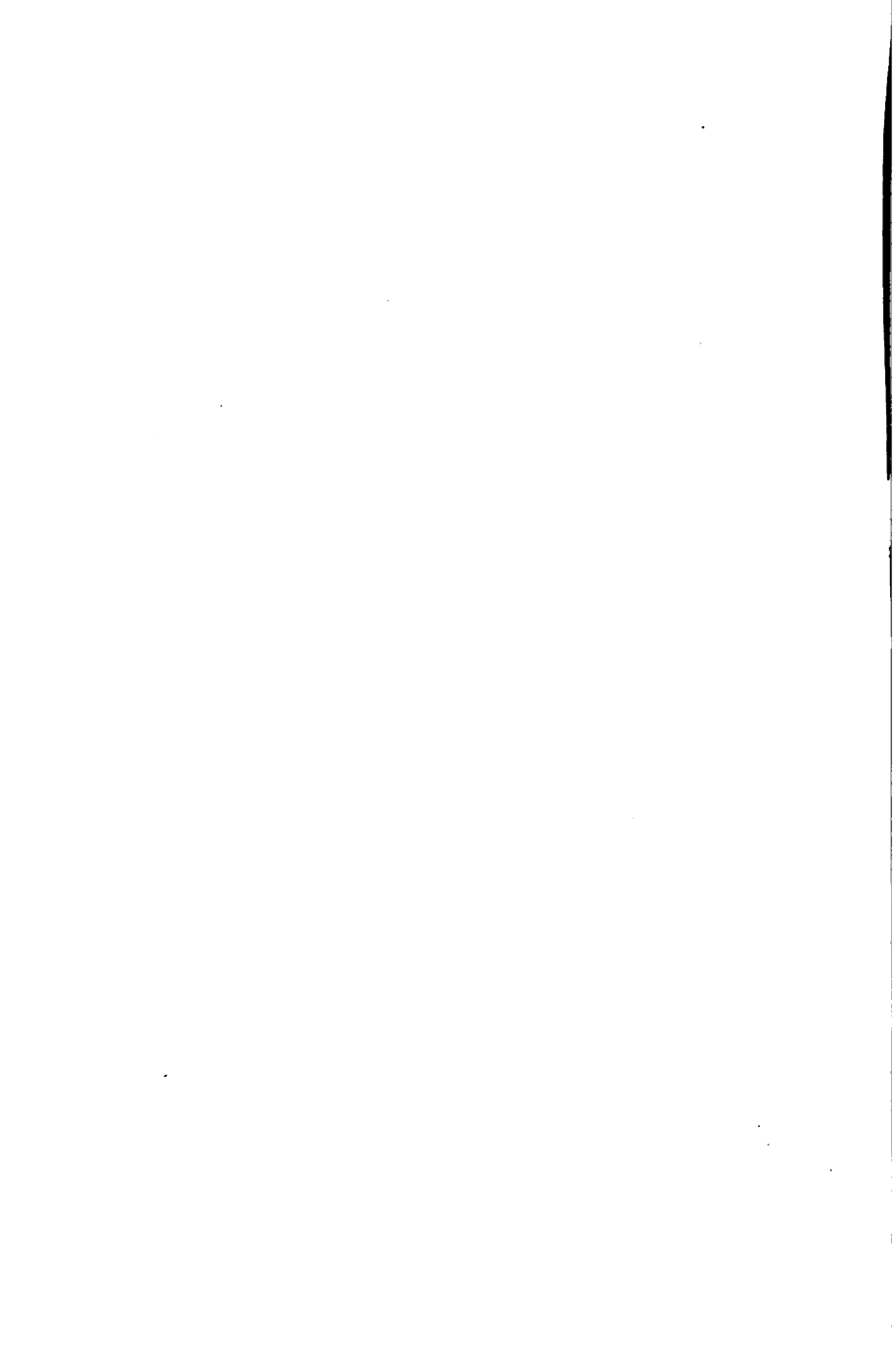


Fig. 2.



and coalesce to form large giant cells in the lumens. Then the basement membrane is destroyed and the proliferation spreads into the surrounding tissue, but the form of the seminal tubules may be retained for a long time, even after caseation and confluence of adjacent nodules. The adjacent parenchyma shows signs of compression (Plate 95, Fig. 1).

Syphilis of the testicle is observed frequently either in the form of diffuse connective-tissue proliferation, leading to atrophy and cirrhosis of the organ, or as circumscribed granulomas about which radiating scars are found. The center is usually uniformly caseous; at times the general structural conditions are retained in an indistinct form in spite of the caseation. The necrotic foci become surrounded by a dense, fibrillated tissue infiltrated with round cells. Giant cells are infrequent. The adjacent parenchyma is traversed by fibrous tissue and shows the changes of a high degree of atrophy. The vessels generally present much proliferation of the adventitia and the intima, often leading to complete closure of the lumen (Plate 95, Fig. 2).

THE FEMALE SEXUAL ORGANS.

The Ovary.—The ovary is covered by a layer of cylindrical epithelial [mesothelial] cells, the germinal epithelium, which is derived from the peritoneum. The germinal epithelium is situated upon a dense fibrous layer—the tunica albuginea. The external parts of the ovary, the cortex or parenchymatous zone, contain the follicles, of which there are three types in the sexually mature woman: namely, (1) the primordial or primitive follicle; (2) the young follicles; (3) the ripe, fully developed follicle ready to burst.

The primordial follicle consists of a single layer of low epithelial cells directly surrounding the egg-cell. Occasional follicles contain two egg-cells.

By far the greater number of primordial follicles perish by atresia: *i. e.*, the egg-cells disintegrate, and later the surrounding epithelium, connective tissue filling the resulting defect.

In growing follicles the originally single layer of follicular epithelium becomes many-layered, and the inner layers produce by liquefac-

tion the liquor folliculi. The connective tissue around the follicle becomes differentiated into a special envelope—the theca folliculi. The liquor folliculi increases in quantity and the follicle enlarges; the egg-cell is embedded in a heap of large follicular cells, the discus or cumulus proligerus or oophorus, which contains a zona pellucida, formed by follicular epithelium, and separated from the egg-cell by a narrow slit—the perivitelline space. The contents of the ovum show distinct yolk granules (deutoplasmic granules) and a nucleus or germinal vesicle which contains an ameboid germinal spot or nucleolus. The external rupture of the follicle follows through increasing rise in the intrafollicular pressure and fatty degeneration of the follicular epithelium. The inner layers of the theca folliculi produce, by enlargement of their cells, the so-called lutein cells. In addition, the ovary consists of a fibrous stroma, which is more cellular and provided with shorter fibers in the cortex than the medullary substance; in the latter lie also a few smooth muscle-fibers from the ligamentum latum.

After rupture the follicle is filled with blood, and forms now the so-called corpus luteum. The blood is gradually absorbed and changed into pigment, and the lutein cells from the inner layers of the theca folliculi, and possibly also from the follicular epithelium, proliferate in the interior of the resulting cavity. In the course of pregnancy the corpus luteum becomes very large (corpus luteum verum), but if the extruded egg perishes unfecundated, then the corpus luteum becomes much smaller (corpus luteum spurium) and disappears gradually. The pigment fades away and the lutein cells undergo hyaline degeneration. Homogeneous, glistening bands pervaded by connective tissue with few fibers remain—the so-called corpus albicans or corpus fibrosum (Plate 98, Fig. 2). In old age the organ becomes exhausted from atresia and rupture of the follicles. The stroma acquires gradually a cicatricial character, and the ovary eventually presents a dry fibrous mass with irregular depressions of the surface.

The Tubes.—The tubes consist of a peritoneal covering, two muscular layers,—an external longitudinal and an internal circular,—and a mucous membrane. The mucous membrane consists of high, ciliated, cylindrical epithelium, and a stratum proprium of round and spindle-shaped fibrous tissue elements. Toward the abdominal end the mucous membrane is raised up into numerous folds, which also form the fimbriæ.

Between the layers of the broad ligament at its external parts lies the parovarium or epoöphoron, a rudimentary organ, which consists of strings of dense cylindrical cell masses, with a fine lumen in the axis, and externally surrounded with muscular fibers and connective tissue.

The Uterus.—The uterus is covered by a peritoneal layer of fibrous tissue clothed with flat epithelium (mesothelium). The uterine tissue proper consists of smooth muscle-fibers which cross each other in all directions, running parallel to the surface only at the periphery. In the vicinity of the blood-vessels are accumulations of connective tissue. In the cervix uteri the connective tissue mixed with elastic fibers predominates at all times of life. In older women,

after the climacterium, the uterine wall itself consists largely of fibrous tissue. There is no submucosa either in the uterus or tubes. The mucosa consists of a soft, cellular, lymphadenoid stratum proprium and an epithelial lining. The epithelial lining of the corpus consists of a single layer of rather short cylindrical cells, situated upon a basal membrane, the nuclei occurring near the base of the cells. During the child-bearing period the epithelial cells carry cilia, the motion of which is toward the vagina.

From the surface of the mucous membrane simple tubular glands (so-called utricular glands) extend into the stratum proprium. In old age these glands become short. In the cervix the glands are not simple tubular, but compound, and even acinous. The surface epithelium contains goblet cells.

During menstruation there is a marked congestion of the mucosa, with the formation of subepithelial hemorrhages, which break through the epithelium. Normally there is no desquamation of epithelium.

At the beginning of pregnancy the cells of the stroma of the mucosa form the decidual cells. The protoplasm increases and the nuclei multiply. Decidual cells are formed in the connective tissue of the wall and in the vicinity of the vessels. The part of the wall of the uterus where the ovum is attached becomes the decidua serotina, and the proliferating part of the uterine mucosa which covers the ovum is the decidua reflexa.

The Vagina.—The vagina consists of an external fibrous wall, containing elastic elements, a smooth muscular layer with longitudinal external and circular internal fibers, and a mucous membrane. The latter consists of many layers of flat epithelium and a tunica propria, which forms papillæ. Normally the vagina is without glands.

The hymen consists of a double layer of flat epithelium disposed upon a stratum proprium with particularly tall papillæ.

THE OVARY.

In acute infectious diseases simple degenerative conditions occur in the ovary, which are designated as parenchymatous oophoritis, in the same manner as analogous degenerations in the kidney are called parenchymatous nephritis. The cells of the follicles are enlarged and clouded, due to the deposition in them of albuminous and fatty granules; the liquor folliculi also may become turbid. Eventually the follicular cells and the ovum disintegrate into a molecular mass, and the follicle passes away. The contents become absorbed and fibrous tissue grows inward from the theca folliculi.

Interstitial Oophoritis.

Chronic inflammations of the ovary occur especially in consequence of chronic gonorrheal infection of the tubes; furthermore in chlorosis, circulatory disturbances caused by heart disease, tumors of the pelvic organs, menstrual disturbances, as well as from incomplete involution of the genital organs after child-birth. With the microscope there is found a high degree of condensation of the albuginea and an increased number of spindle-shaped cells in the stroma. The organ may become smaller on account of cicatricial contraction. The vessels usually are thicker than normal and there are often hyaline changes in the intima. The contraction may lead to a general sclerosis of the ovary, and, owing to the destruction of the follicles, it falls into a state of premature senility. When intact follicles remain, the condensation and sclerosis of the albuginea may prevent their rupture, the liquor folliculi increases, and there results cystic degeneration of the ovary. The excessive growth of single follicles under such conditions may give rise to large unilocular cysts.

An acute infectious oophoritis may be caused by various bacteria, such as staphylococci, streptococci (especially in the puerperium), gonococci, more rarely pneumococci, colon bacilli, typhoid bacilli, as well as a number of anaerobic organisms. The bacteria enter mostly by way of the lymphatics, and cause, in the first place, a purulo-fibrinous perioophoritis. Destruction of the germinal epithelium allows the bacteria to traverse the tunica albuginea, and on reaching the stroma abscesses are formed occupying smaller or larger portions of the organ (suppurative oophoritis). Follicles filled with pus corpuscles are found in such cases. Pyogenic microbes, especially gonococci, may be deposited in the corpora lutea, whence abscesses may originate (corpus luteum abscess).

Tuberculosis of the ovary is found in general miliary tuberculosis and in localized genital tuberculosis. The

nodules are scattered about in the medullary substance as well as in the cortex. The germinal epithelium corresponding to the location of tubercles occasionally proliferates and sends solid buds or irregular tubular masses into the stroma below. Epithelioid and giant cells may be scattered about in the ovarian tissue in addition to being present in circumscribed nodules. The follicles in the vicinity of tubercles are destroyed, and the epithelium is loosened and disintegrates. Confluence of smaller nodules may give rise to large caseous areas.

The ovary is a frequent seat of cystic tumors, the structure of which, as well as the structure of carcinoma, sarcoma, dermoids, and teratoma, is discussed in the volume on "General Pathologic Histology."

THE TUBES.

Hemorrhages into the mucosa and other layers of the tubal wall may result from venous obstruction, especially in consequence of torsions of the tubes. In sections there are found larger and smaller extravasations, also numerous leukocytes loaded with blood pigment; and in older hemorrhages the connective-tissue cells and muscle-cells of the tubal wall may be crowded with changed blood corpuscles and granular pigment. At times hyaline degenerations of the tubal wall may induce circumscribed necroses in the tube.

Catarrhal inflammations of the oviduct lead to a marked infiltration of the mucous membrane with leukocytes and to a marked dilatation of the vessels. The epithelium shows an increased number of goblet cells with mucoid metamorphosis of the protoplasm, partial desquamation, swelling, and fatty changes of single cells. Hemorrhages may occur in the deeper layers; the stratum proprium is edematous, its spaces widened, and the folds of the mucous membrane swollen. In long-continued catarrhal processes the folds grow thicker and thicker, and come in contact

PLATE 96.

FIG. 1.—Erosion of the Anterior Lip of Os Uteri in a Child.

× 37. 1, Cylindrical epithelium of cervix ; 2, extension of cylindrical epithelium on lip of os uteri ; 3, glandular depression on external surface of os uteri ; 4, transition into flat epithelium (5).

FIG. 2.—Remains of Decidua in Uterus.

× 88. 1, Musculature of uterus ; 2, vascular spaces ; 3, decidua cells.

with one another. After desquamation or atrophy of the epithelium adhesions of the folds may take place, which may lead to stenosis, and even to complete occlusion of the tubal orifice. In the depths of the adherent walls may be formed recesses and spaces, clothed with epithelium, in which accumulations of secretion may produce small cysts (Martin's salpingitis pseudofollicularis). The closure of the uterine end may lead to circumscribed hypertrophies of the tubal musculature, appearing as myomatous nodules, which are found by microscopic sections to consist of muscular tissue, the center usually containing spaces clothed with epithelium (Chiari's salpingitis isthmica nodosa).

The entrance of pus microbes, especially streptococci and gonococci, causes purulent inflammations of the oviducts. The submucosa and the epithelium are then densely infiltrated with pus corpuscles. Extensive epithelial desquamation takes place and the shed masses are mixed with pus in the lumen, which often becomes greatly dilated. The spaces between the folds are filled with pus cells. Even the muscular coat may be infiltrated with pus, mural abscesses may result (mesosalpingitis purulenta), and suppuration may extend to the serosa and the pelvic connective tissue.

When the abdominal end of the tube is closed in chronic tubal inflammations, the accumulations of fluid in the lumen give rise to sausage-shaped and retort-like enlargements of the tube (hydrosalpinx, sactosalpinx serosa). There is usually marked atrophy of the mucous membrane, and flattening, and even complete disappearance, of the epithe-

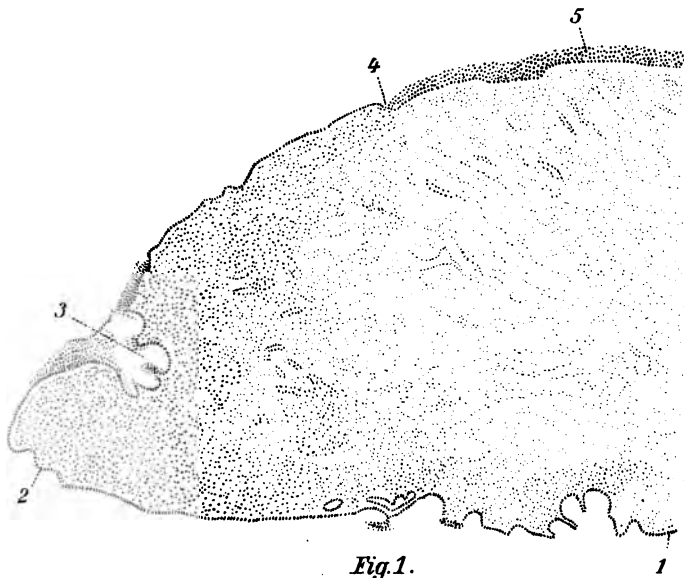


Fig. 1.

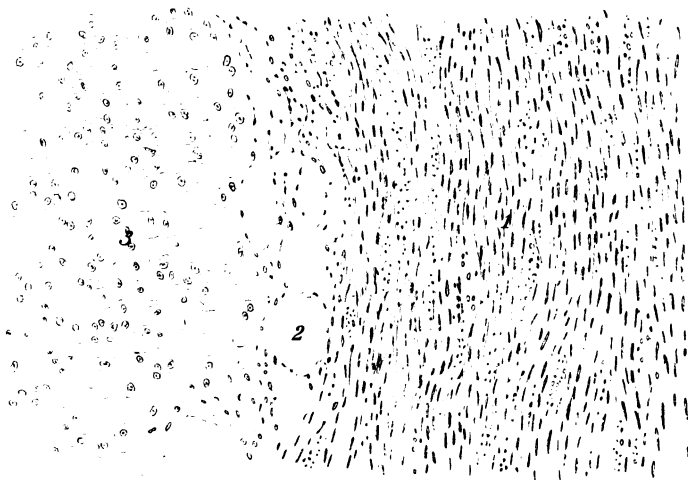


Fig. 2.



lium. When a closed tube is filled with pus, the condition is called *pyosalpinx* or *sactosalpinx purulenta*. The mucosa is destroyed to a large extent; the lymph spaces of the wall are widened and filled with pus microbes.

Tuberculous salpingitis may be primary or secondary, due to extension from the uterus. Tuberculous endosalpingitis is characterized microscopically by the presence of typical tubercles in the mucosa, at first usually in the tips of the folds. At first the surface epithelium is retained. The subjacent nodules in the stratum proprium are formed by epithelioid and giant cells and are surrounded by dense accumulations of round cells (Plate 98, Fig. 1). The epithelium is gradually destroyed. Occasionally it seems as if the epithelium took part in forming giant cells. The nodules enlarge and break through into the lumen, coalescing with one another; the abdominal end being closed, the tube soon becomes filled with caseous masses. Often there is an early extension of the process to the muscularis and the serosa, and eruption of multiple nodules on the serous surface.

The primary tubal tumors are polypoid papillomas of the mucosa, carcinoma, sarcoma, and myoma.

THE UTERUS.

The most frequent lesions in the uterus are inflammatory changes in the mucous membrane or endometrium. Endometritis may appear in very different forms, anatomically as well as clinically. It is found most frequently in chronic irritations of all kinds in the pelvic organs, and also in many constitutional deviations. The simplest forms find their expression in hyperplasias and hypertrophy of the mucosa. In the first case there is a new formation of glands in the mucous membrane: the surface epithelium sends new tubules downward or existing glands divide dichotomously or send out branches. This is shown microscopically by a closer approximation of the various

PLATE 97.

FIG. 1.—Endometritis Glandularis Cystica of Cervix Uteri. $\times 30$. 1, Musculature; 2, cystic dilatations of cervical glands filled with mucus.

FIG. 2.—Endometritis Glandularis Chronica. $\times 40$. Uterine glands greatly proliferated, lengthened, and convoluted.

glands to one another. It is usually assumed that in the normal organ the distance between the uterine glands is equal, on an average, to four or five times the transverse diameter of the glands, but in this condition the glandular tubules appear side by side and the stroma is apparently greatly diminished. Often the proliferation affects only the deeper parts of the glands, the ends of which appear forked (endometritis hyperplastica glandularis). The hypertrophic glandular form of endometritis, on the other hand, shows itself in an increased growth in length and thickness of the preexisting glands. The tubules appear elongated, the lumen dilated, and the epithelial walls enlarged. At the same time there is an increased production of mucus from the transformation of epithelial cells into goblet cells, and the surface epithelium is richly infiltrated with round cells. Little by little the interstitial tissue becomes traversed by glands throughout its entire thickness, the lower ends of the tubules resting upon the muscular layer (Plate 97, Fig. 2). On account of the greater resistance offered to the growth by the muscle, the glandular tubules become convoluted, and even twisted like a corkscrew. Because the epithelial proliferation continues after the downgrowth meets with obstruction, invaginations occur, so that in cross-sections there may be two and even three concentric epithelial rings, one within the other. Obstruction to the outflow of the increased secretion leads to cystic dilatations and ampullæ in some of the tubules, which then are filled with mucus. The resistance of the muscular coat is not absolute, even in non-malignant proliferations, and occasionally the elongated

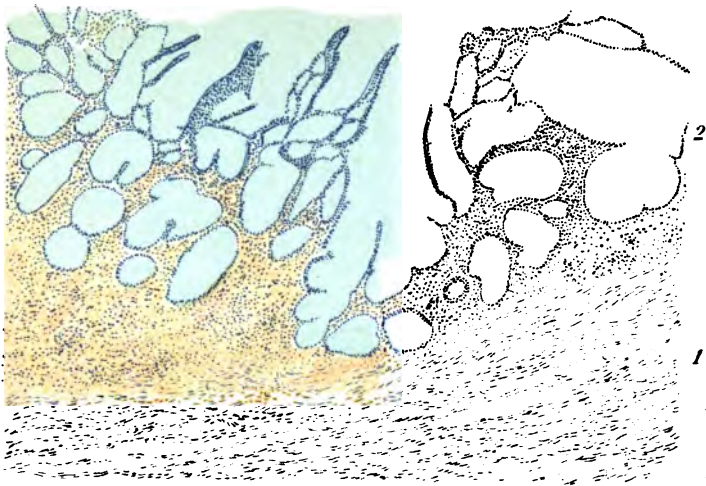


Fig. 1.

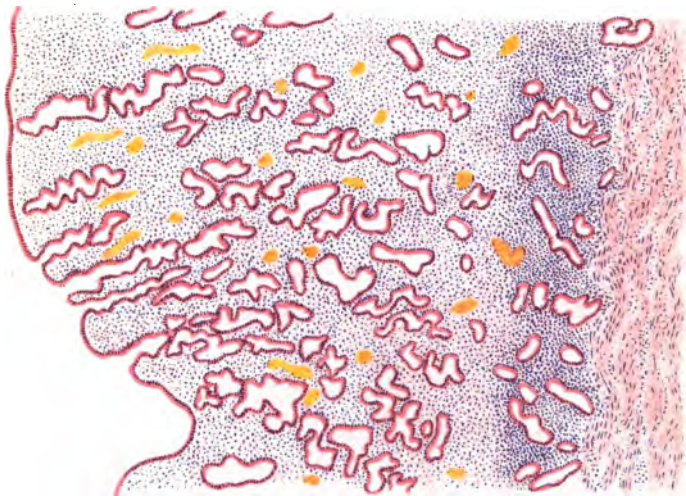


Fig. 2.



and tortuous tubules extend into the inner muscular layer ; but such appearances alone do not warrant the conclusion that the process is malignant. The appearances of invagination in such intramuscular glandular proliferations especially are of practical value in the differential diagnosis of glandular hypertrophic endometritis and the early stages of carcinoma of the endometrium.

In contrast to the glandular form, interstitial endometritis is characterized by an increase of the cellular elements of the stroma. The distances between the tubules appear increased, and often the microscopic field shows but few glands. The process needs not be uniform in all parts of the stratum proprium ; it is usually more pronounced in the deeper layers, so that the lower terminations of the glands appear further separated than the superficial portions, and thus the glands undergo displacement and acquire an oblique course. In the beginning there are circumscribed or diffuse infiltrations of small mononuclear lymphocytes. The fixed cells also multiply ; they are greatly swollen, and the cell bodies may be ten times as large as the normal stromal spindle cells, the fibers appear short and sparse, and the resulting epithelioid cells recall very distinctly the formation of the normal decidua. The density and the regularity of the decidual cells prevent mistakes. In the later stages there occurs a shrinking in the interstitial tissue, due to cicatricial contraction of the newly formed cells. Numerous closely approximated connective-tissue fibers are produced, the protoplasm of the stromal cells is reduced to small spindle-shaped formations, and the fibers may coalesce throughout large areas into a sclerotic, almost non-nucleated tissue. This results in a firm attachment of the mucosa to the muscular layer, and the glands appear shortened, atrophic, and often obliquely placed. The constriction of single gland tubules by new tissue may cause the accumulation of secretion and cystic dilatations with flattening of the epithelium.

In acute interstitial endometritis there occurs at times

in the spaces of the stroma a more pronounced accumulation of albuminous fluid, which may be mixed with red blood cells. The menstrual congestion of the mucosa now usually leads to the separation of continuous shreds of the cellular mucous membrane, and sometimes to the expulsion of the mucous membrane in toto (membranous dysmenorrhea). If the mucous membrane shows the decidua-like proliferation of the cells of the stroma, it is spoken of as a menstrual decidua.

In chronic interstitial endometritis there may be circumscribed proliferations of the interstitial tissue and a jutting forward of the mucous membrane in the form of polypoid masses. As these masses often contain displaced and cystic tubules, larger cystic polypi may arise in which may be extensive cavities.

Tuberculosis of the endometrium is rather rare, occurring either primarily or secondarily, especially as the result of extension from the peritoneum. In the corpus uteri two forms may be distinguished: (1) Miliary nodules scattered about in the mucosa, and (2) a diffuse caseous form (endometritis caseosa); to which may be added still a third form in the cervix uteri, namely, the papillomatous (E. Fränkel).

In the last form the proliferating stratum proprium forms numerous long finger-like processes, covered with epithelial cells, and at the base of which the nodules are found. In the first form of miliary tuberculosis of the mucous membrane the tubercles are distributed in the mucosa, whose surface epithelium usually is normal. The tubercles are formed from epithelioid and giant cells derived from the fixed connective-tissue cells of the stroma, and there is usually a well-marked reticulum. At times the uterine glands, especially the deeper portions, are involved in the formation of the nodules, and in this case giant cells are formed by the glandular epithelium. As the tubercle grows, it reaches the surface and elevates the epithelium, the caseous center ruptures, and there results a small ulcer

with undermined margins. The confluence of numerous granulomas may give rise to larger ulcerations with caseous floors. It is exceedingly rare to find an eruption of nodules and caseation in the fibromuscular wall of the uterus.

One of the most common changes in the cervical canal is catarrhal inflammation. It is characterized by the production of large masses of mucoid and mucopurulent secretion. Microscopic sections consequently show a marked dilatation of all the glands, often associated with increase in the number and size of the glandular elements (Plate 97, Fig. 1). All the cervical glands are changed into large spaces with numerous recesses; in many, closure of the mouth has led to cystic dilatations and ampullæ. The sections show numerous apparently closed cavities, which correspond to the transversely or obliquely cut branches of the glands. These often reach into the fibromuscular layer. Nearly all such spaces appear filled with a homogeneous mucoid material that stains blue with hematoxylin and is formed from the retained secretion. The epithelium is greatly flattened, in some places absent; desquamated cells may be present in the lumen, and goblet cells may be recognizable in the lining. The stratum proprium generally appears reduced to very narrow strips and islands, greatly infiltrated with round cells, and wholly absent between the dilated glands. In the acute, purulent forms of cervical catarrh of recent gonorrheal infection, the interstitial tissue is broad, infiltrated with pus corpuscles, which also appear in the glandular spaces, mixed with mucus.

Especially in women that have borne children, the vaginal portion of the cervix often presents sharply circumscribed, bluish-red spots, which bleed very readily. These are called erosions. Microscopic examination, however, shows that it does not concern loss of substance in the epithelium, which is present everywhere, but that in the place of the normal flat epithelium are variously sized islands of

cylindrical cells. Erosion of the portio cervicalis is consequently a replacement of the flat epithelium with cylindrical epithelium of the same character as that of the cervical mucous membrane (Plate 96, Fig. 1). Often this change is observed in newly born girls under circumstances that exclude the presence of any special disease and indicate that it is a developmental anomaly. The cylindrical epithelium, in place of reaching, as usual, only to the margins of the lips of the cervix, passes beyond this limit and creeps up on the vaginal aspect, where it forms branching recesses of the type of the cervical glands. The transition between cylindrical epithelium and flat epithelium is quite sharp; the cylindrical cells stop at a certain point, being continued only as the basal layer of the rete Malpighii (Plate 96, Fig. 1).

In the adult three forms of erosion are recognized, according to the condition of the epithelium. Between these forms are, of course, numerous transitions:

1. The simple erosion, in which the cylindrical epithelium covers the stratum proprium in a single smooth layer, the epithelial cells presenting the same relations as in the cervical canal. They are arranged according to the type of a palisade, the nuclei being located near the base.

2. The follicular erosion in which the vaginal portion is not only covered with cylindrical epithelium externally, but recesses are formed in the stratum proprium. By constriction of the necks of the glands, secretions accumulate and form vesicular cavities, which often result in extensive cystic dilatations projecting as globular masses under the epithelium (ovula Nabothi) and causing unevenness of the surface of the erosion. The fluid in such cysts may be rendered turbid by the admixture of pus.

3. The papillary erosion appears macroscopically as an irregular, warty surface, and microscopic sections show numerous ingrowths of the epithelium in the form of branched tubules; the mouths of the glandular formations, however, do not lie on a level with the surrounding

mucous membrane, but project high above it. A proliferation of the stratum proprium has taken place, which has pushed the surface epithelium outward in the form of branching projections. The apices of the papillæ often show losses of substance, especially when the seat of recent inflammatory changes.

All forms of erosion are susceptible of healing: from the margins, flat epithelium slides in over the cylindrical epithelial layer, and it often happens that the glandular recesses are shut off from the surface, and thus form in the stratum proprium closed cavities lined with epithelium.

Attention has been called to the papillary character of tuberculosis of the cervical portion of the uterus.

A common condition in women of advanced age and past the menopause is the so-called apoplexia uteri. The uterine mucosa is swollen, velvety, deep red, loosened, and infiltrated with blood. The microscopic examination shows the absence of inflammation. The stratum proprium and the superficial muscular layers are infiltrated with blood corpuscles, and the superficial epithelium is in part destroyed. Sections of the uterine wall show a marked disease of the arteries. The walls are very thick, the lumen often almost completely closed, and the thick media may be hyaline or calcareous; in short, there are present the changes of advanced endarteritis obliterans. Pronounced arteriosclerosis elsewhere in the body is usually not observed. Undoubtedly this condition of the arteries explains the hemorrhages into the mucosa, which Simmonds regards as agonal or preagonal. The whole uterine wall usually shows great diminution of muscular elements, which are replaced by fibrous tissue.

Metritis.

Outside of the puerperium most cases of acute inflammations of the uterine wall (acute metritis) are caused by the gonococcus. The softened, enlarged organ shows microscopically accumulations of round cells, especially

PLATE 98.

FIG. 1.—**Tuberculous Salpingitis.** $\times 35$. 1, Apices of transversely cut folds of the mucosa, deprived of epithelium and caseous; 2, tuberculosis giant cells. The adjacent mucosa markedly congested.

FIG. 2.—**Hyaline Degeneration of Corpus Fibrosum of the Ovary.** $\times 72$. The fibrous tissue filling the shrunken follicle transformed into homogeneous, glistening, convoluted masses, simulating caseous material. The surrounding tissue greatly indurated and fibrous; the many vessels have thick walls.

around the vessels, and the muscular and fibrous tissues are edematous, the interstitial spaces enlarged. Dense accumulations of leukocytes may lead to abscesses in the uterine wall, in the contents of which gonococci may be found (Madelener). Chronic metritis is characterized by circumscribed or diffuse increase of connective tissue in the uterine wall. Between the new fibrillæ, which lead to a gradual shrinking of the whole organ, are found mast cells in large numbers (Orth). (Compare volume on "General Pathologic Histology," "Inflammation.")

In the puerperium suppurative inflammations of the endometrium and myometrium are caused by infection, most frequently with streptococci. The inner surface of the uterus is covered by a membranous, necrotic, greenish-yellow mass, often also by purulent material. Hence there is an innermost layer of necrotic decidual cells, between which are dense, cloud-like masses of streptococci. This layer borders on a layer of pus corpuscles. The venous vessels, often greatly dilated, are filled with purulent thrombi, mixed with streptococci, and the walls are infiltrated with leukocytes. The muscular walls also show diffuse purulent infiltration. All lymph spaces are filled to distention with pus cells and masses of streptococci. Extension often takes place to the peritoneum, which becomes covered with a purulo-fibrinous exudate.

In puerperal involution of the uterus the greatly en-

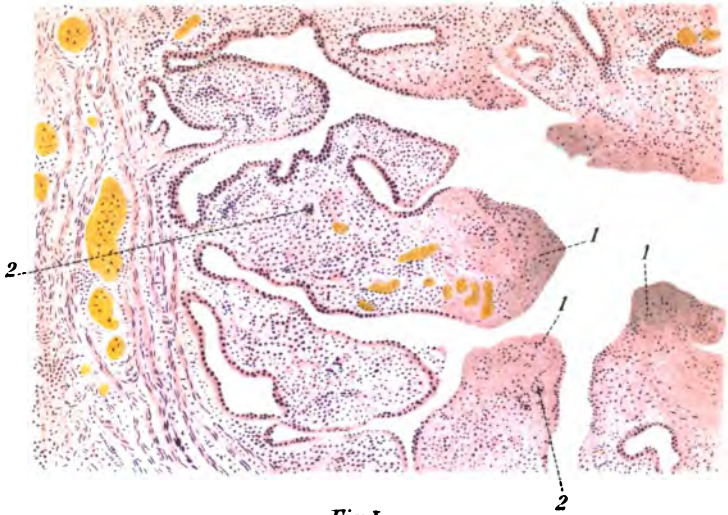


Fig. I.

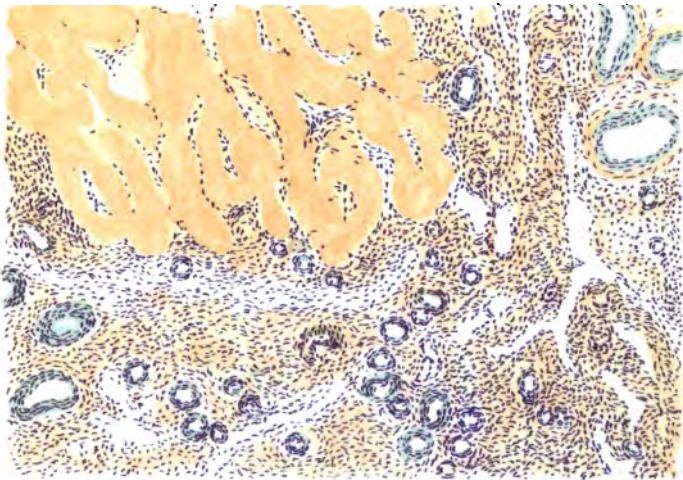


Fig. II.



larged muscle-cells¹ are reduced to normal size by fatty changes in the protoplasm. There is no destruction of muscle-fibers, and the parts of the decidua which are not expelled are gradually transformed into normal stroma. Under certain conditions this involution may fail to take place, and the decidua may persist in places. Instead of the normal stroma of the mucous membrane, are found polygonal decidual cells closely packed. The surface epithelium and the glands are absent in such places, in the immediate vicinity of which normal mucous membrane may have formed again. Chorionic cells also may remain in the uterus after the expulsion of the fetus and the placenta. These cells may retain their typical structure for a long time or undergo a hyaline degeneration. They project as villous masses above the level of the mucosa, and are designated as placental polypi. From their epithelial covering there develops occasionally the so-called malignant syncytioma (carcinoma syncytiale, sarcoma deciduochoriocellulare, deciduoma, deciduosarcoma, chorioepithelioma—Marchand). Although the original elements of this tumor are derived from the fetal portion of the placenta, they have the power to proliferate in the maternal organism and to form metastases (see volume on "General Pathologic Histology").

Of other tumors in the uterus the most frequent are myoma and fibromyoma. Sarcomas and carcinomas also occur, and they are discussed in the volume on "General Pathologic Histology."

Special mention must be made of adenomyomas, because they occur only in the uterus. These tumors occur especially in the dorsal wall of the uterus and at the tubovarian angles, and they are composed of smooth muscle-

¹ Sanger gives the following dimensions of the muscle-cells of the uterus:

Four to six hours post partum,	158.3 μ long and 12.2 μ broad.
Three to four days " "	117.4 " " " 10.5 " "
Thirteen " " "	64.4 " " " 6.7 " "
Fifty-five " " "	21.2 " " " 5.45 " "

cells and peculiarly arranged epithelial tubules. Among the latter it is usually possible to distinguish a principal canal, into which empty numerous collecting tubules arranged in rows or like the teeth of a comb, so that there results a complete system of epithelial tubules with terminal bulbs and ampullæ. Often several systems of this kind are united by means of tortuous canals. Underneath the epithelium there is found, as in the uterus, a cellular stratum proprium, which borders directly on the muscular tissue. Von Recklinghausen has shown that these formations are derived from the Wolffian body. Similar epithelial tubules without myomatous growth have been traced to remnants of the Wolffian duct (Klein).

THE VAGINA.

The vagina may be the seat of simple catarrhal and of ulcerative inflammations. In the former there are, in addition to marked capillary injection, diffuse subepithelial infiltrations. The epithelial cells are loosened and there is increased desquamation of its upper layers. Between the cells of the Malpighian layer are found numerous leukocytes in the act of migration. The vaginal secretion contains usually large masses of bacteria, which are also found in heaps among the superficial epithelial layers. When defects develop, these may be covered with croupous exudate. The puerperal colpitis especially is characterized by croupous exudation ; but genuine diphtheria of the vagina, caused by Löffler's diphtheria bacillus, has been observed also.

Colpitis emphysematosa, or colpohyperplasia cystica, is applied to a peculiar inflammation of the vagina marked by the formation of subepithelial gas cysts. In microscopic sections the latter appear as sharply circumscribed, rounded cavities, situated immediately under the basal layer of the epithelium and extending into the stratum proprium. The epithelial covering is thinned and flat-

tened. In the vicinity of the cyst wall occur numerous giant cells of the tuberculous type. [The giant cells are undoubtedly foreign body giant cells in their nature. Colpitis emphysematosa is caused by gas-producing anaerobic bacilli.]

Tuberculosis of the vagina is usually associated with tuberculosis elsewhere in the genital organs, and begins with the formation of typical nodules in the papillary body, which later break through and are changed into ulcers.

THE CENTRAL NERVOUS SYSTEM.

The **dura mater** consists of parallel layers of connective-tissue fibers, among which are numerous elastic fibers. The spinal dura mater is covered both externally and internally by a single layer of flat cells. The cerebral dura mater arises from the fusion of the spinal dura mater and the internal periosteum of the spinal canal, and it forms the internal periosteum of the cranium. It contains also elastic fibers in its connective tissue and is covered internally with a double layer of flat cells. Between the connective-tissue fibers lie numerous lymph spaces clothed with a delicate epithelium.

The **arachnoid** is composed of a network of connective-tissue bundles; over the spinal cord it is very thin, but over the brain it may be as much as forty microns in thickness; it is covered with a flat epithelium and sends numerous bands of bridges to the pia mater. The pia mater covers all the elevations and depressions of the brain and cord and extends inward as a sheath around the vessels that penetrate into the interior. An external fibrillar and an internal more vascular layer may be distinguished. In the brain it forms prolongations, known as tela superior and as plexus choroidei, which extend into the cerebral ventricles. Its surface is covered with a single layer of low epithelial cells.

As regards the finer histologic structure of the central nervous system, especially as concerns the course of the fibers, reference must be made to special works on histology. At this time is indicated only the general histologic structure of the nervous system.

In the brain and cord there is distinguished the gray and the white substance. The gray substance is composed of ganglion cells and their processes (dendrites and neuraxones); the white substance consists of nerve fibers. The ganglion cells [neurocytes] are divided into multipolar and bipolar (the so-called unipolar possess T-shaped divisions) according to the number of their processes. The body is large and consists of peculiar groups of fibrillæ and granules; the

nucleus is vesicular, poor in chromatin; the nucleolus is large. The ganglion cells have two kinds of processes: (1) A nervous process or neuraxone, and (2) numerous protoplasmic processes or dendrites. In some cells—as, for example, in Purkinje's cells of the cerebellum—the dendrites are developed to an extraordinary degree. The neuraxone either remains naked throughout its entire extent or it becomes surrounded by a layer of myelin, a fatty material also known as the medullary sheath. The myelin sheath at certain points shows interruptions or constrictions, the so-called nodes of Ranvier, beneath which the neuraxone presents a slight biconical swelling. Nerve fibers composed only of axones and myelin sheaths are found only in the central nervous system. In the peripheral part of the nervous system the myelin sheath is covered externally by another membrane, Schwann's sheath or neurilemma, a fine structureless layer which at certain points upon its internal surface carries oval nuclei surrounded with some protoplasm.

The supporting tissue of the central nervous system is not formed by fibrous tissue, as in other organs, but by a peculiar tissue, the glia tissue or neuroglia. It consists of cells and fibers. Two groups of cells are distinguished, the ependyma cells, which clothe all the cavities, and the so-called astrocytes. Both possess very fine fibrillar processes, some of which are short, and such cells occur especially in the gray substance, while others are longer, and these occur principally in the white matter (Deiters' cells). In the spinal cord the latter type usually presents a principal process, which passes to the surface of the cord, where it ends in a foot-like enlargement.

In the peripheral nervous system the fibers which are provided with myelin sheaths and neurilemma become inclosed by connective-tissue fibrillæ which unite with one another to form the endoneurium. Each single bundle of fibers is surrounded by a dense fibrous layer—the perineurium. Many such bundles are inclosed by fibrous sheaths, which hold them together, and are known as epineurium.

THE DURA MATER.

One of the commonest changes in the dura mater is chronic productive pachymeningitis. It occurs especially in old age associated with atrophy of the brain, in chronic alcoholism, and in general paralysis. As it usually is associated with hemorrhage into the newly formed tissue, and generally develops upon the inner surface of the dura, it is designated as pachymeningitis interna hæmorrhagica. In the earliest stages of the process the inner surface of the dura is covered by a fine, veil-like, easily removable membrane. The microscopic examination shows that it

consists of a fibrinous network, the threads for the most part running parallel with the connective-tissue fibers. Between the threads lie leukocytes, single and in groups. At this time the epithelium on the inner surface of the dura is usually present. As in similar inflammations in other serous membranes, one frequently finds delicate fibrinous threads under the loosened epithelial cells. Before long, however, partial loss of epithelial covering is followed by the growth of young connective-tissue cells from the inner layers of the dura into the fibrinous membrane.

The cells are large, spindle-shaped or polygonal, with abundant protoplasm, and they first arrange themselves in rows between the epithelium of the dura and the fibrinous deposit. Simultaneously young vascular sprouts emerge from the dura and extend into the deposit as solid buds, which later are hollowed and filled with red blood cells. Very soon extraordinarily rich vascular networks are formed and the membrane assumes a deep red appearance. The walls of the vessels always remain very thin, consisting largely of epithelial cells, so that hemorrhages take place freely either from rupture of the walls or by diapedesis. It seems evident that slight variations in pressure may cause hemorrhages under these circumstances. [Melnikow-Raswedenkow ¹ has pointed out that the increasing thickness of the internal elastic coat offers mechanical conditions that favor the occurrence of hemorrhages.] Red blood cells pass out into the fibrinous network, where they disintegrate into pigment masses that in part are taken up by wandering cells. The fibroblasts gradually form connective-tissue fibers which run parallel with the fibers of the dura; but as the vessels remain for considerable time, new hemorrhages occur again and again, which lead to increased deposits in the new membrane (Plate 99, Fig. 1). New connective tissue and new vessels grow out into the extravasated blood, and in this way the new layer may

¹ "Ziegler's Beiträge," 1900, XXVIII, 226.

PLATE 99.

FIG. 1.—**Pachymeningitis Interna Hæmorrhagica.** $\times 45$. 1, Thick, fibrous dura ; 2, newly formed membrane or inner surface ; 3, pigment masses and numerous young vascular sprouts ; 4, cross-section of a newly formed vessel ; 5, concentrically lamellated amyloid body.

FIG. 2.—**Pachymeningitis Spinalis Syphilitica.** $\times 66$. 1, Dura ; 2, gummosus granuloma with caseous center and with giant cells (4) ; 3, artery with thick, infiltrated wall, and almost complete closure of lumen.

acquire considerable thickness. The oldest portions eventually become fibrous and sclerotic, the vessels are obliterated, and the limits between the membrane and the dura become indistinct. For a long time the new tissue is marked by the presence of blood pigment of all kinds, diffusible, granular, amorphous, partly intracellular, partly extracellular, and also hematoidin crystals. The younger amorphous pigment may give the iron reaction for a long time. In this way thick layers of scar tissue may arise. When large vessels are present, more extensive hemorrhagic extravasations may occur between the lamellæ of the fibrous tissue and give rise to large accumulations of blood that may compress the brain (hematoma of dura mater). Formerly these hemorrhages were explained on the score of traumatism, and it was thought, further, that the entire membrane might develop upon the basis of a traumatic hemorrhage. In the earliest stages, however, the inflammatory nature of the process is always evident. [The earliest changes are seen not infrequently in infectious diseases without having produced any symptoms during life.] Complete resorption of the blood cells, and the resulting pigment in hematomas of the dura mater, render the fluid colorless and serous, and this condition is termed hygroma of the dura. In the later stages the inner layers of the new fibrous lamellæ often contain large, globular, concentrically lamellated bodies, which are stained blue with iodine and sulphuric acid, and therefore called cor-

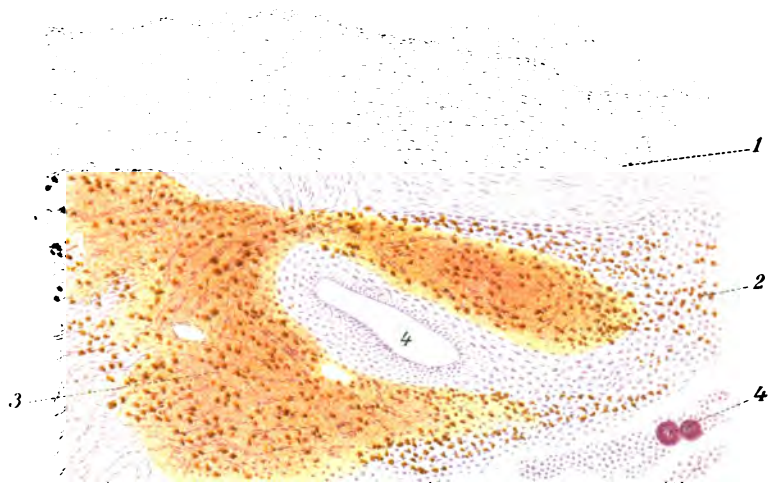


Fig. 1.

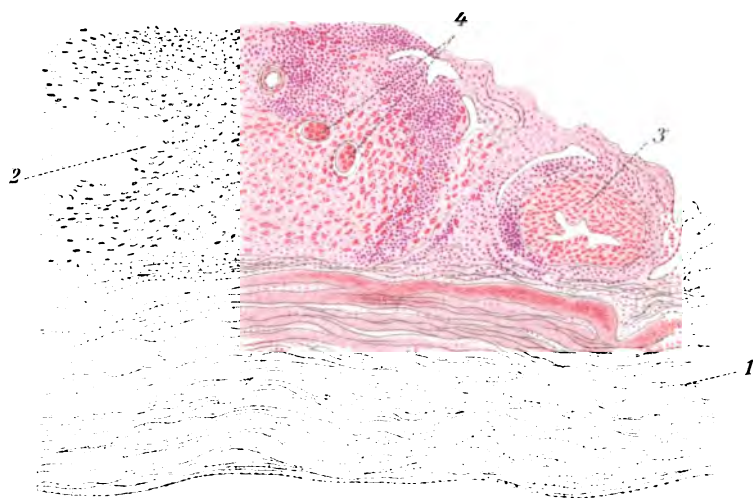


Fig. 2.

pora amyloidea. These bodies probably develop from the coalescence of cells, and in the interior may be seen traces of one or more nuclei (Plate 99, Fig. 1).

Suppurative pachymeningitis occurs as the result of extension from the pia mater. The inner surface of the dura is then covered with a purulent layer, often mixed with fibrin, the epithelium is destroyed, and pus cells may penetrate between the fibrous lamellæ and cause partial softening of the dura.

Tuberculosis of the pachymeninx is probably always the result of extension either from the pia mater or from tuberculous caries of the cranium or spinal column.

In rare cases syphilis appears in the spinal cord and cerebral dura, either as a more circumscribed granuloma or as diffuse infiltration and increase in thickness. Upon the surface cicatricial masses may form, inclosing typical gummous nodules with caseous centers surrounded by giant cells, epithelioid cells, and round cells, the periphery consisting of hard fibrous tissue. The vessels in the neighborhood show the well-known endarteritic changes (Plate 99, Fig. 2).

THE PIA MATER.

Acute purulent leptomeningitis is caused mostly by diplococci, and occasionally by streptococci and staphylococci; in rare instances, especially in the newborn, it is caused by the colon bacillus. Microscopically there is seen purulent exudation into the subarachnoid space and the tissue of the pia mater, which at times is very extensive. In the early stages fibrinous threads are often scattered among the pus corpuscles; occasional filaments are seen also in the vessels of the pia, and even in the superficial vessels of the adjacent brain substance. At the same time the micro-organisms between the pus corpuscles are often brought into view. The blood-vessels, especially the small pial veins, are dilated to the utmost. Marked stasis, with peripheral disposition of the leukocytes, is evident. The

PLATE 100.

FIG. 1.—Acute Suppurative Cerebral Leptomeningitis. $\times 55$. 1, 1, Two cerebral convolutions; between them the pia mater infiltrated with purulent exudate (2); 3, 3, pial vessels, dilated to the utmost.

FIG. 2.—Chronic Leptomeningitis. $\times 78$. 1, Cerebral convolution; 2, fissure in which lies pia mater infiltrated with cells and some pigment granules; 3, vessels with infiltrated adventitia passing into brain substance.

cellular accumulations outside of the vessels occasionally show two layers of different density: an external, composed mostly of leukocytes, and an internal, less dense, and lighter layer, in which there may be recognized, in addition to pus corpuscles, large spindle-shaped and rounded cells—fibroblasts. The purulent exudate usually follows closely the course of the pia, especially at the convexity, and there is also more or less infiltration of the pial sheaths of the cortical vessels. The lymphatic spaces of the adventitia are filled with leukocytes, occasionally also with fibrinous threads. If a purulent meningitis has existed for some time, fresh preparations will show fatty changes, fragmentation, and other evidences of disintegration in the pus corpuscles.

Chronic inflammations of the spinal and cerebral pia-arachnoid are recognized by areas of condensation in the arachnoid, which may present also deposits or fine villous outgrowths of fibrous tissue. In the pia are diffuse or circumscribed infiltrations with round cells, and this is especially marked in the sheaths of the vessels that penetrate into the cortex. Fresh teased specimens show the adventitial spaces filled with round cells with small amount of protoplasm, and also with larger cells that are filled with fatty and pigmentary granules. In sections, infiltrated walls may be traced far into the brain substance. Among the round cells are found also small brown pigment granules (Plate 100, Fig. 2).

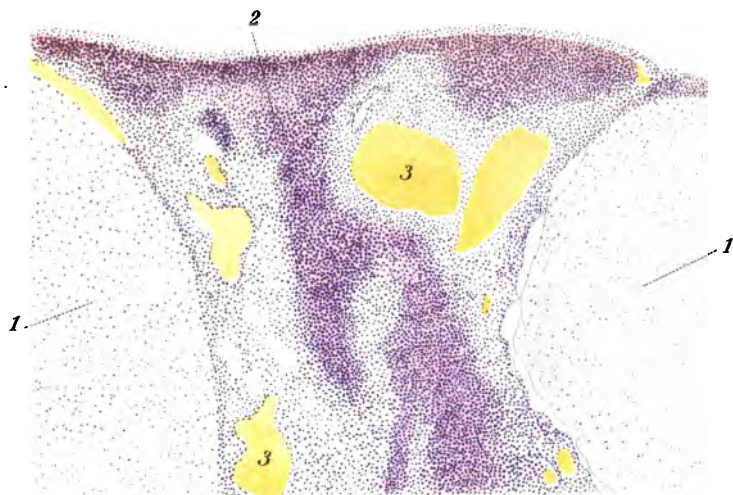


Fig. 1.

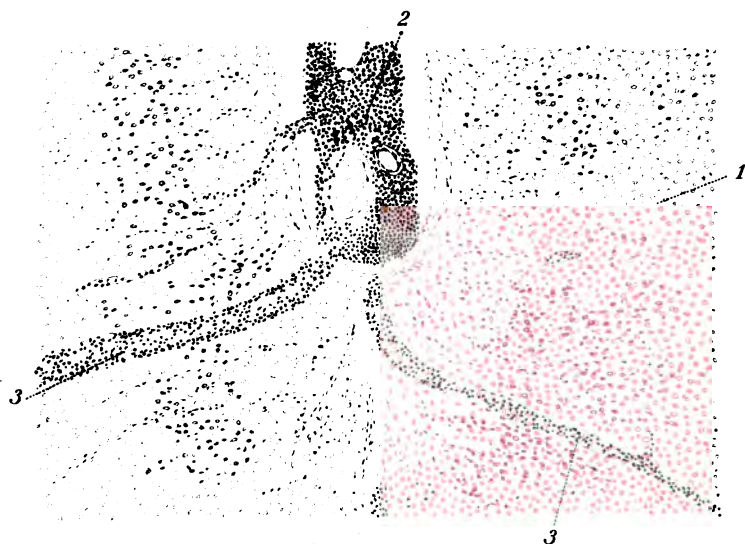


Fig. 2.

In contrast to the purulent leptomeningitis, the tuberculous form is localized especially at the base of the brain, about the chiasma, the infundibulum, in the Sylvian fissures, and also about the pons and medulla oblongata; hence it is often called basilar meningitis. The nodules appear mostly in the course of the pial vessels, and, in addition, a gelatinous, turbid exudate spreads into the meshes of the pia-arachnoid. The relation of the nodules to the vessels is made out easily with the naked eye, and it becomes particularly clear in the microscopic sections (Plate 101, Fig. 1).

The arachnoidal spaces and the tissue of the pia are infiltrated with leukocytes in great numbers, among which are occasional fibrinous threads, and often also large epithelioid cells in fair numbers. The walls of the arteries and the veins nearly always show a marked infiltration, often extending through all the coats, including the internal elastic layer, as has been described previously (Vol. I, p. 40, Plate 10, b). The characteristic nodules usually lie in immediate contact with the walls of the vessels, and cannot, as a rule, be distinguished from the adventitia. Occasionally they surround the vessels in the form of a crescent (Plate 101, Fig. 1). Even when the clinical duration of the disease is only from nine to ten days, there is beginning caseation in the centers. In instances of longer duration the caseation extends rapidly, so that one often finds extensive, confluent nodules with continuous caseous centers.

At the periphery of the necrosis there are mostly radially arranged spindle-shaped or rhombic epithelioid cells. On account of the rapid course of basilar meningitis, giant cells are few; usually they are absent entirely. The process may extend to the superficial layers of the brain by way of the vascular sheaths. Frequently the rapid caseation leads to rupture of blood-vessels and circumscribed hemorrhages, with destruction of the superficial brain substance (tuberculous meningo-encephalitis).

PLATE 101.

FIG. 1.—**Tuberculous Leptomeningitis.** $\times 30$. (Section through fossa Sylvii.) 1, 1, Cerebral gyri; 2, pia mater infiltrated with cells; 3, periarterial tubercle with cerebral caseation; 4, cross-sections of larger arteries with acute inflammatory changes in walls.

FIG. 2.—**Syphilitic (Gummos) Leptomeningitis.** $\times 30$. 1, Cerebral gyri; pia mater infiltrated with cells; 3, caseous center of granuloma extending to adventitia of a large artery (4); 5, internal elastic coat lost in proliferating fibrous tissue.

Occasionally the disease extends by direct continuity to the choroid plexus as well as to the ependyma of the ventricles. Tubercles in the ependyma may be seen with the naked eye as fine granulations, especially by oblique light. Microscopic sections often show quite early stages in the tubercles, which may consist only of epithelioid cells, the overlying ependymal cells being lost entirely.

Within the nodules, tubercle bacilli are usually easily demonstrable in large numbers, but in the diffuse infiltrations they are few and scattered.

Syphilitic leptomeningitis is characterized by a diffuse, gelatinous exudate and circumscribed nodules that tend to regressive changes, but the whole process is chronic in its course, and the lesions have a fibro-cicatricial character. Nodules with caseous centers and fibrous margins occur in the vicinity of the vessels, especially the larger arteries. The relation to the vessels is very distinct and intimate, the granulomas first appearing in the adventitia of the pial arteries (Plate 101, Fig. 2). The vessel walls present the obliterating processes described previously (Vol. I, p. 42). Often thrombosis takes place. The cicatricial condensation extends from the nodules to the adjacent pial tissue, and may lead to considerable new fibrous tissue and increase in volume. Sometimes the superficial cerebral layers are infiltrated, and the caseo-cicatricial masses may extend into the brain, so that cerebral substance and meninges become blended inseparably (Plate 101, Fig. 2).

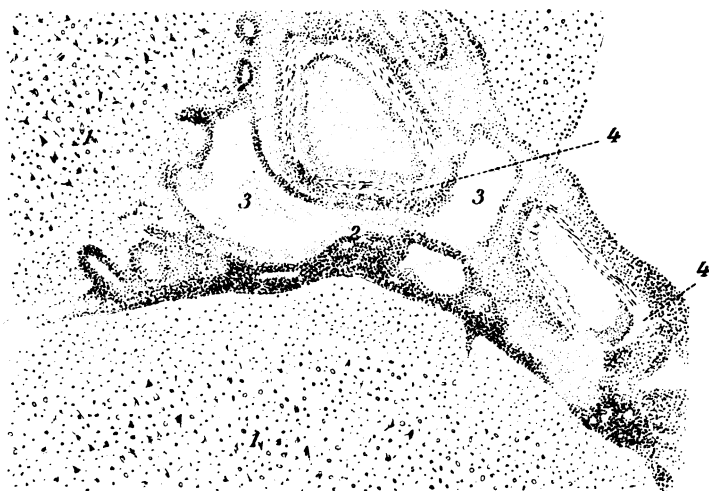


Fig. 1.

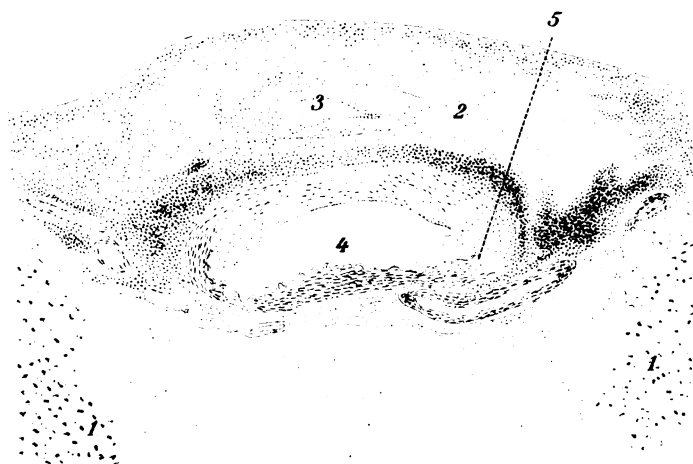


Fig. 2.



THE BRAIN AND SPINAL CORD.

In considering the histologic changes of the central nervous system no attention can be given to so-called system diseases and their genesis and relationship. In this place it is intended to describe only the general histologic conditions which may be common to nervous diseases of different clinical course and different gross alterations. On this account it is not necessary to separate the diseases of the brain from those of the spinal cord, so far as the histologic changes are concerned.

Obstruction to the return of the venous blood from the central nervous system or parts thereof gives rise to an edematous infiltration of the nervous matter. The spaces between the nerve fibers then appear broadened, the glia fibers are finely granular, the axones are much thicker than normal on cross-section. The medullary sheaths are either compressed and relatively thin, or swollen from the imbibition of fluid. When longer continued, the edema leads to degeneration in the medullary substance, which is broken up into fragments. Disintegration of the axones also becomes apparent: in longitudinal sections swellings appear at various intervals, and segmentation and vacuolation of the substance takes place. Degenerative processes in the nervous system are followed, as a general rule, by processes of resorption, which are discussed in the following. Concussions of the brain and cord also give rise to circumscribed infiltrations of fluid. In the gray substance there is simultaneously a disintegration of ganglion cells, preceded by a peculiar rearrangement and clumping of the fibrillar and granular substances.

Hemorrhage.

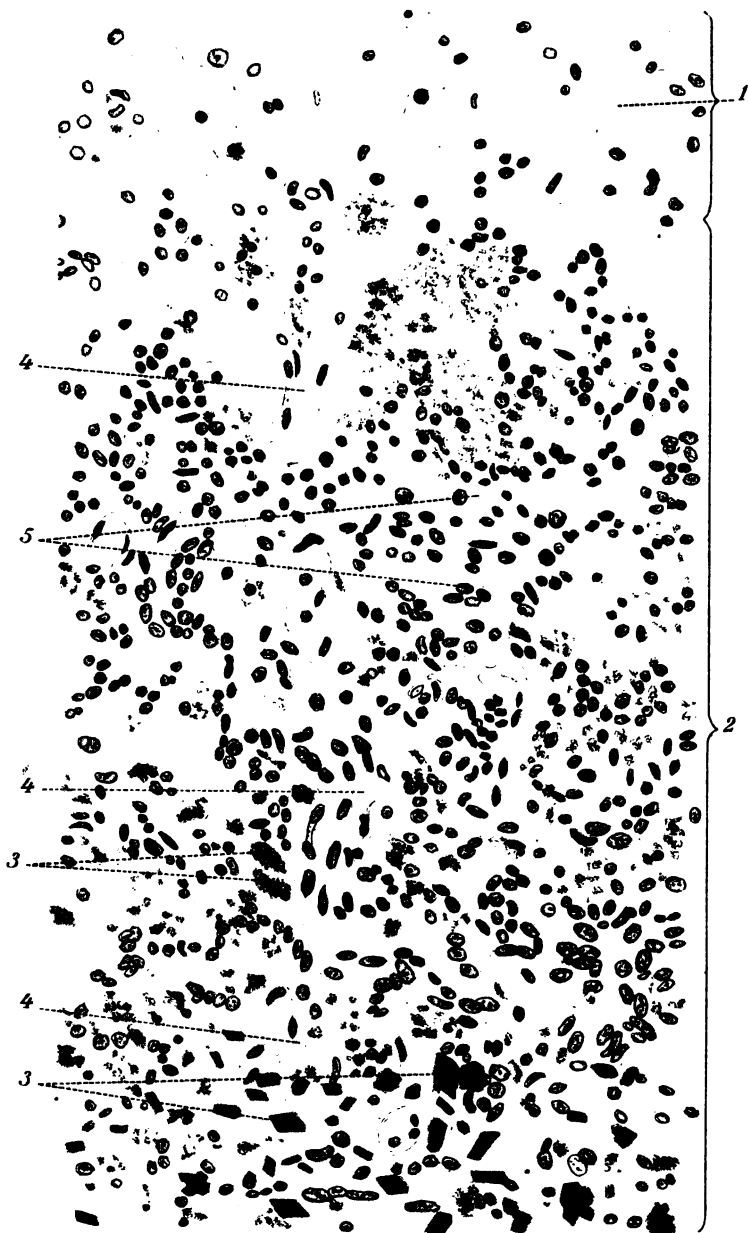
Hemorrhage into the brain, from whatever cause, either in consequence of spontaneous rupture in sclerosis of the vessels or from increased pressure, as well as from traumatic influences, presents a series of characteristic micro-

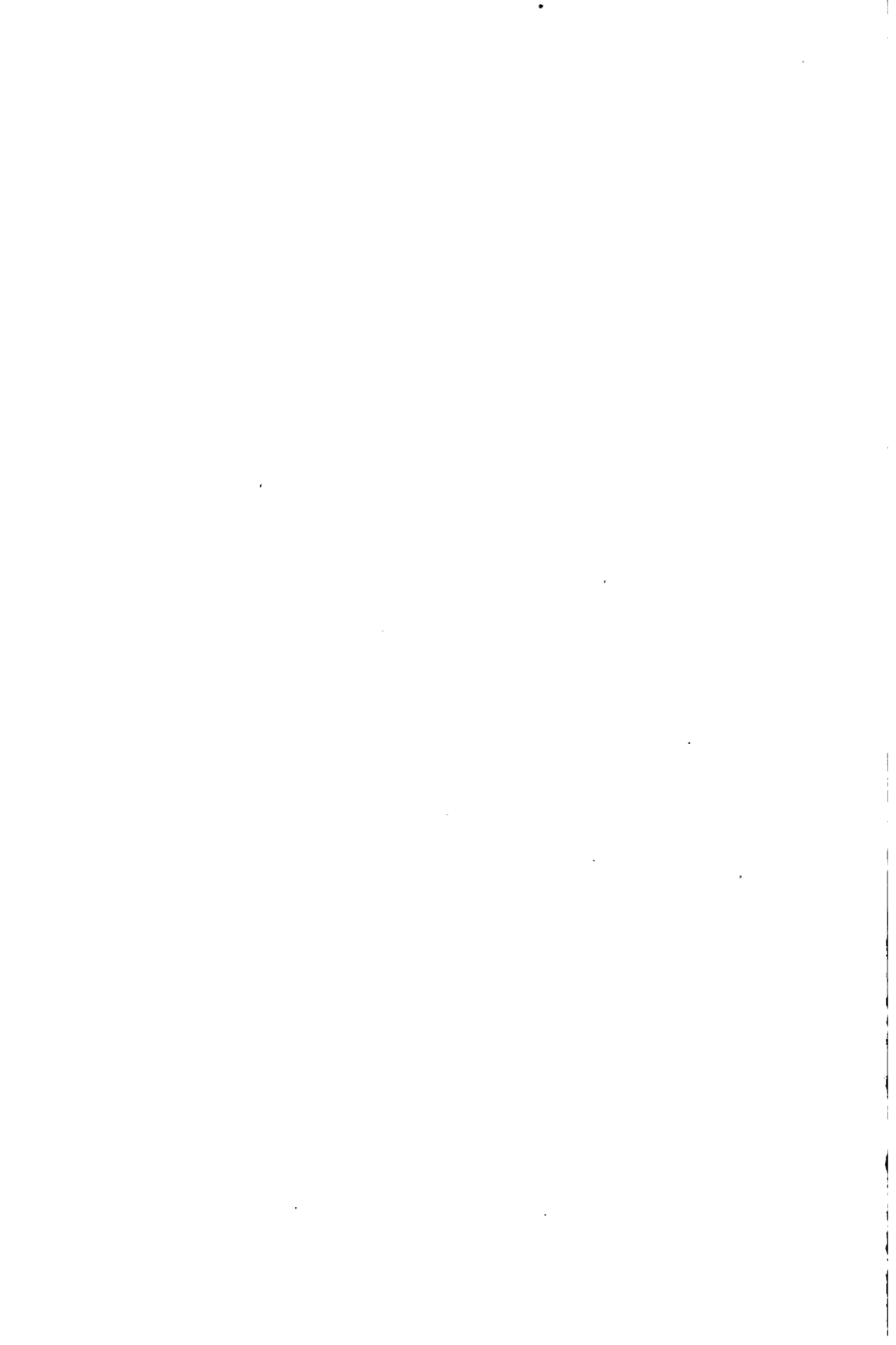
PLATE 102.

Old Apoplectic Focus from Cerebral Cortex. $\times 67$. 1, Brain substance at margin of focus ; 2, apoplectic focus occupied by young connective tissue and blood pigment ; 3, amorphous and crystalline pigment ; 4, young vascular sprouts ; 5, young connective tissue with epithelioid cells and round cells.

scopic changes, which vary according to the age of the hemorrhagic focus. In the examination attention must be directed, on the one side, upon the brain substance, and, on the other, upon the extravasated blood. As elsewhere in the body, extravasated blood passes through a series of changes which gradually render it absorbable and convert it into pigment masses.

Every extravasation of blood into the substance of the central nervous system causes disintegration of nervous tissue to an extent depending on the size of the hemorrhage. The nerve fibers give rise to especially typical products of disintegration. The axones are deprived of the medullary substance, which swells up and coagulates. In teased specimens from an early stage isolated fragments of nerve fibers are seen with more or less numerous, peculiar, spindle-shaped or circular swellings. These are the so-called varicose axones. The medullary substance is compressed about the axones at places, and at the same time it is swollen. The varicosities appear doubly contoured under moderate enlargement, and the axones usually show some very fine, refractile fat granules. There are also seen naked axones, wholly deprived of medullary sheaths, and having single contours. The broken-up medullary substance generally takes the form of single globules and balls, which are seen to appear first upon the varicose axones as hernial protrusions. The free masses of medullary substance are characterized by their double contour, and are designated also as myelin droplets. At the same time there is usually free fat present as larger or smaller single contoured, refractile droplets.





At this early stage the red corpuscles are wholly intact, but as early as the second day diffusion of the hemoglobin from the erythrocytes begins to stain the surrounding tissues with a yellowish tinge. As the surrounding tissue is edematous on account of the abnormal pressure, the fluid of the edema takes up the diffused coloring-matter and may stain larger areas of the brain or spinal cord. As early as the third day new cellular elements appear at the margin of the hemorrhagic focus. They are large, rounded, protoplasmic cells with one (not infrequently two) deeply stained granular nuclei. It is not settled whether these cells are derived exclusively from leukocytes or whether or not fixed cells, such as the endothelial cells of the perivascular lymph spaces, may not also participate in their production. It is also not at all unlikely that other cells—such as connective-tissue cells from the vascular adventitia, glia cells, and even ganglion cells—each furnish a contingent to the cellular accumulations that form around foci of hemorrhage and softening and gradually extend into their interior. At all events, the cells have marked phagocytic properties, in that they take up into their interior detritus of all kinds, including that from the blood, and thus they subserve the purposes of resorption. As their protoplasm is capable of a very considerable enlargement, they may be called, with v. Recklinghausen, “contractile cells,” without thereby expressing any definite opinion as to their origin. These cells take up very soon the detritus of the disintegrated brain tissue, and many of them become filled with very minute, yellowish, glistening fat droplets, so that the nucleus is no longer recognizable, at least in fresh, unstained cells. They are now called “granule cells,” “fat granule cells,” and also “fat granule spheres.” The granule cells predominate for some time in the microscopic picture, and they are altogether characteristic of all processes in the central nervous system which begin with disintegration or degeneration of nervous tissue, and they may be found for years about

PLATE 103.

FIG. 1.—From Margin of Apoplectic Focus in Cerebrum. $\times 300$. Thirty days old. 1, Shadows of red corpuscles ; 2, contractile cells with fat vacuoles ; some cells have two nuclei ; 3, amorphous pigment free ; 4, cells containing blood corpuscles.

FIG. 2.—Old Apoplectic Scar in Cerebrum. $\times 78$. 1, Brain substance ; 2, fibrillar, acellular connective tissue with dark pigment granules ; 3, young vessels with thin walls.

such foci, which, in the mean time, have been replaced with scar tissue. It seems that, having loaded themselves with detritus, the cells wander into the lymphatics ; at all events, they are found, especially in the later stages, principally in the lymphatic spaces of the adjacent vessels. In this way may arise lasting dilatations of the lymphatic vessels, recognizable microscopically as fine, tubular cavities in the neighborhood of old foci of softening or of hemorrhage—a condition which has been termed *état criblé*. Myelin droplets and larger fragments of neuraxones may be taken up by these cells. In the fixed and stained sections the fat and the myelin are extracted, and the cells that contained these substances appear penetrated in a sieve-like manner by numerous rounded vacuoles, the nuclei being now visible (Plate 103, Fig. 1).

But the contractile cells also subject the blood to their phagocytic activity. After the third day cells inclosing red blood cells are found at the margins of the hemorrhagic focus. Some cells may contain only a few corpuscles in addition to fat ; others may be crowded full with corpuscles, which gradually undergo an intracellular digestion. If the corpuscles contain hemoglobin at the time they are taken up, then they gradually shrink to small, deeply colored pigment masses of irregular, angular form. The blood cells that remain free lose their hemoglobin by diffusion ; at first they swell up, and the biconcave disks assume a globular form. In sections they appear as pale or colorless objects, the so-called “ shadows,” which even do not

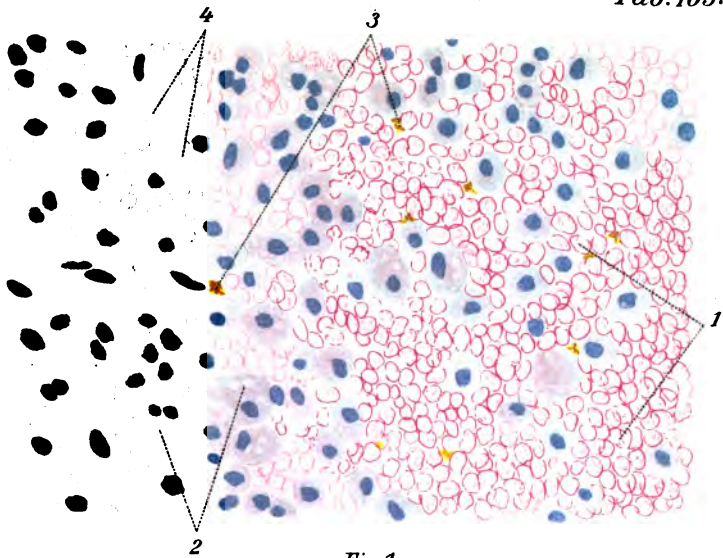


Fig.1.

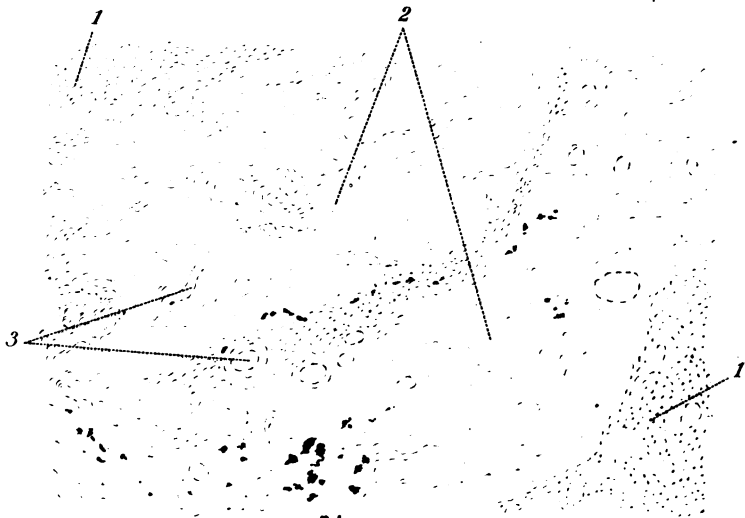


Fig.2.

stain with eosin. Later a shrinking takes place in these corpuscles also. At first minute impressions appear, often extending around the whole periphery (Ecker and Virchow's "marginal bodies"), and later larger invaginations occur, producing forms that may resemble scutellated and cup-shaped bodies. The corpuscles may be taken up at this stage by contractile cells and destroyed by them, or they are gradually dissolved while extracellular.

The coloring-matter of the blood diffused into the surrounding tissue may undergo two distinct changes: (1) a morphologic, and (2) a chemical.

The first is made evident by the gradual disappearance of the diffused pigment from the area of disintegration, except as regards the contractile cells, in which it is quite evident that the pigment is accumulating; for, beginning at about the tenth day, there appear at the margins of the focus rounded and angular pigmentary masses and scales, which, at first coarse, later become smaller and smaller. Hence pigment granules are deposited in the contractile cells partly as the result of taking up red blood cells, partly from concentration of the diffused pigment. At about the same time it is possible to make out a chemical change in the blood pigment, in that the iron it contains becomes susceptible to microchemic reactions with ferrocyanid of potassium and hydrochloric acid, as well as with ammonium sulphid, *i. e.*, hemoglobin gives origin to the hemosiderin of Neumann (see "General Pathologic Histology," "Pigment").

Little by little the exclusively intracellular pigment masses are set free by disintegration of the corresponding cells. Free blood pigment is found in the margins of general hemorrhages after about the eighteenth day. Later the iron of the pigment is split off, and the pigment granules, which become smaller and smaller, no longer give the iron reaction, but constitute the iron-free hematoidin. A part of the pigment is transformed into rhombic hematoidin crystals, which very rarely are found within the cells.

PLATE 104.

FIG. 1.—Focus of Softening in Cerebrum. $\times 200$. 1, Disintegrated brain substance with contractile cells (2), some of which have two nuclei; 3, new vessel filled with red cells.

FIG. 2.—From a Spot of White Softening in the Cerebrum. $\times 320$. Fresh, teased specimen. 1, Fat granule cells; 2, myelin droplets; 3, varicose axones; 4, free fat.

FIG. 3.—So-called Millary Aneurysm of a Small Artery near an Apoplectic Focus. $\times 80$. Fresh, teased specimen. 1, Aneurysmal dilatation of small arterial vessel; the adventitia filled with fat droplets.

In the mean time new elements wander into the apoplectic focus from the adjacent intact cerebral tissue, especially numerous young vascular sprouts, as well as cells derived from the fixed tissue, principally connective-tissue cells or fibroblasts. The fibroblasts are characterized by polygonal or spindle-shaped outline, and large vesicular nuclei. Young vessels and fibroblasts gradually extend into the defect caused by the hemorrhage, at the same rate as the detritus is removed by absorption. Consequently the margins of the hemorrhage at a certain stage consist only of a young granulation tissue, throughout which is scattered free granular and crystalline pigment.

In the margins of the adjacent healthy cerebral (or spinal) substance appearances are seen indicating condensation on the part of the neuroglia, the fibers of which form a dense network; the cells swell up and send out numerous prolongations ("spider cells"); but regeneration of the broken-up nervous elements in the focus of disintegration does not take place. The resulting defect is bridged by connective tissue formed by the fibroblasts; but as the new tissue often does not suffice to fill the entire space, large hemorrhages frequently give rise to cystic cavities, which are filled with a thick fluid, usually of a rusty appearance, on account of the pigment, and provided at the periphery with a more or less distinct wall. In old apoplectic foci

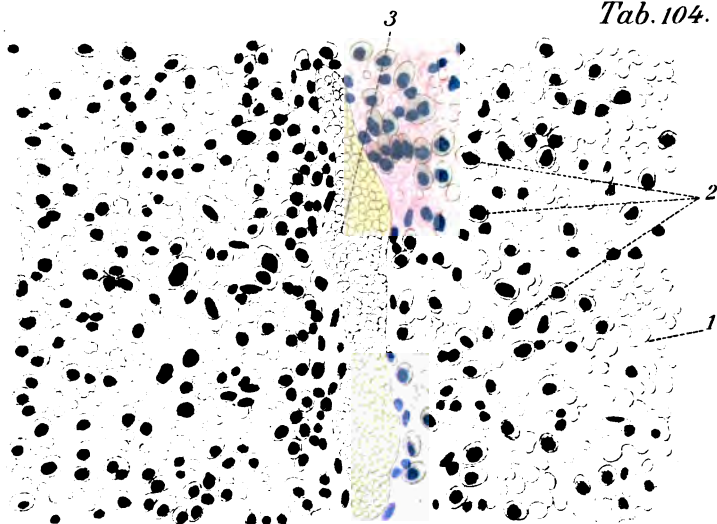


Fig. 1.

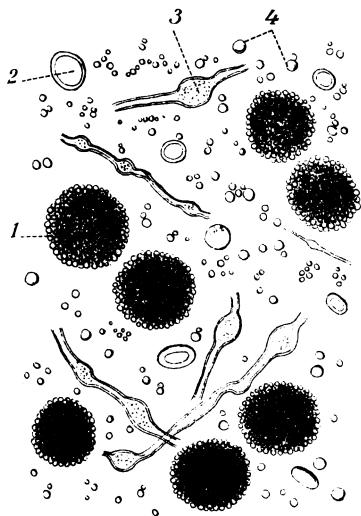
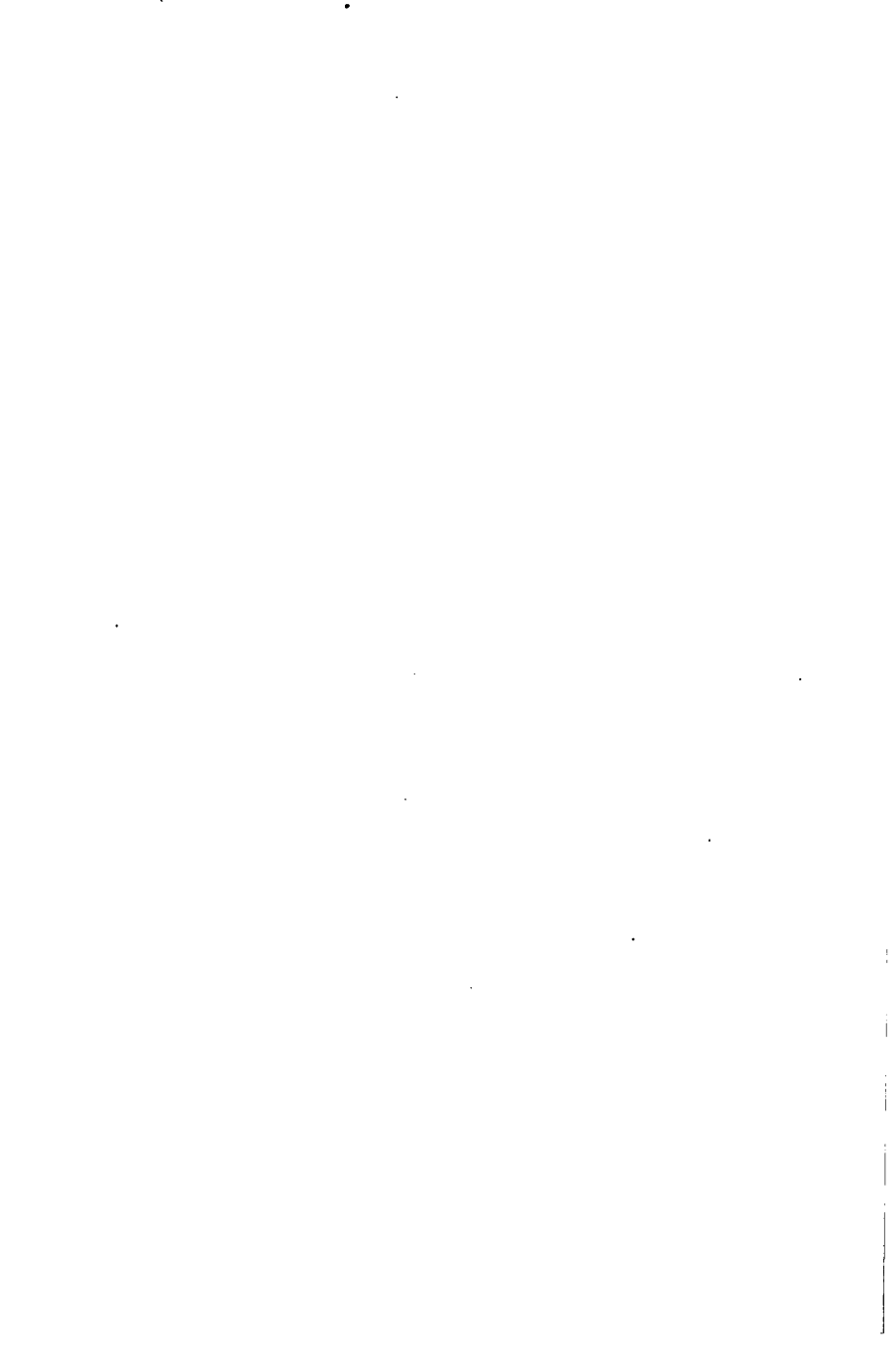


Fig. 2.



Fig. 3.



the wall consists of a dense, fibrillated fibrous tissue, which is poor in cells and dotted with pigmentary collections. Smaller foci may be replaced wholly with such tissue (Plate 103, Fig. 2).

Toward the lumen of the cyst the connective tissue may assume a myxomatous character, the cells being larger, connected with one another by radiating processes, the intervening spaces being filled with fluid.

Frequently changes in the blood-vessels are found in the vicinity of apoplectic foci, especially recent ones. The middle-sized and smaller arteries, when isolated, may present multiple spindle-shaped and ampullar enlargements. Virchow designated these dilatations as miliary aneurysms, and Charcot has pointed out their frequent, and almost constant, association with cerebral apoplexy. But one must distinguish between true and false miliary aneurysms. In the first form there is a genuine dilatation of the lumen of a small vessel, associated with partial disappearance of the media; the cells of the intima, and also the adventitia, usually being infiltrated with fat granules, the lymphatic spaces of the adventitia containing granule cells (Plate 104, Fig. 2). Genuine aneurysms may be simulated by small spindle-shaped swellings of the smaller vessels, due to accumulations of fat granule cells and detritus in the adventitia. Naturally, there is now no dilatation of the lumen, but rather narrowing.

The rust-colored or yellow, usually depressed areas in the surface of the hemispheres, the so-called "plaques jaunes," owe their origin to circumscribed hemorrhages, mostly traumatic, and present microscopically the structure of an old apoplectic focus.

Encephalomalacia.

Embolism of the cerebral arteries by thrombotic masses leads to infarction and local death of the brain substance, because most parts of the brain are provided with endarteries.

PLATE 105.

FIG. 1.—**Margin of Embolic Cerebral Abscess.** $\times 78$. 1, Abscess cavity with leukocytes; nuclear fragmentation; 2, cerebral substance; 3, vessels with cell infiltration of lymph sheaths.

FIG. 2.—**From the Vicinity of a Solitary Tubercle of Brain.** $\times 160$. 1, Cerebral substance; 2, caseation in tubercle; 3, epithelioid cells; 4, round cells.

While local death in all other organs is followed by a solidification due to coagulation of the albuminous substances of the cells, local death in the central nervous system is succeeded by softening, which often leads to liquefaction of the tissue.

Consequently cerebral infarcts are designated as encephalomalacic foci (foci of softening), and, according to the color, there is recognized a white and a brown or yellow softening, the color depending, however, upon the absence or presence of blood. After the death of the cerebral substance there follows a breaking-up of the elements quite similar to that described in recent hemorrhagic areas. Swollen, varicose axones, myelin drops, and numerous phagocytic granule cells are found. If, at the same time, blood-vessels rupture, hemorrhage takes place into the softened district and red encephalomalacia results. This is the analogue of the red or hemorrhagic infarct of other organs. In the absence of hemorrhage the color of the nervous tissue and of the products of its disintegration predominate—white encephalomalacia. In larger areas of softening small extravasations may occur only at the margins; and as the pigmentary changes described in the foregoing take place, the focus assumes a brownish tinge (Plate 104, Figs. 1 and 2).

The further histologic changes in the softened area are the same as in the apoplectic focus. The broken-up nervous elements are absorbed largely by means of contractile cells (Plate 106, Fig. 1). Regeneration does not take place. Young, vascularized granulation tissue grows in from the

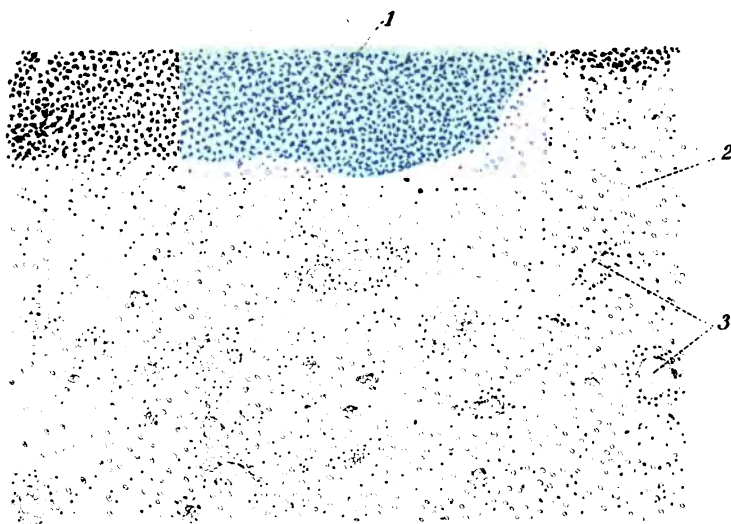


Fig. 1.

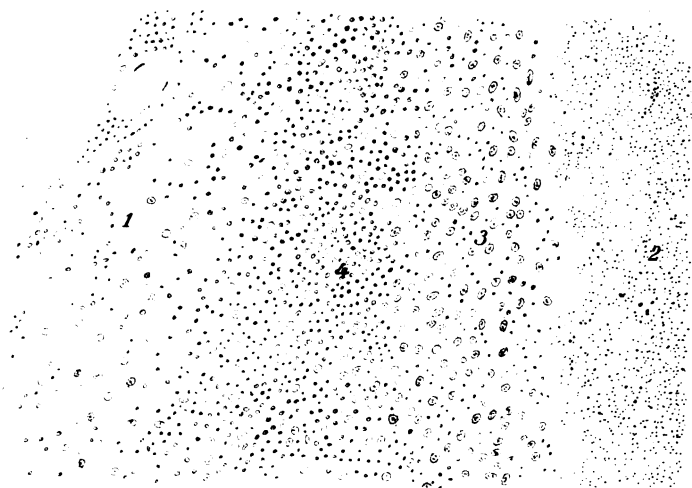


Fig. 2.

margins and substitutes a part of the area, forming, in the course of time, a connective-tissue capsule. More extensive softenings frequently result in encapsulated cysts filled with a turbid fluid resembling buttermilk.

Inflammations.

Suppurative, tuberculous, and syphilitic inflammations may extend from the cranium and from the cerebral membranes into the brain. Primary acute encephalitis may arise in various infectious diseases, especially in pyemia, endocarditis, articular rheumatism, anthrax, etc. In the simple cases there are found small foci of infiltration about the cortical vessels, the pial sheaths of which are infiltrated with round cells, and frequently micro-organisms (diplococci, streptococci, anthrax bacilli) may be demonstrated in the vascular adventitia. Usually the piaarachnoid is involved at the same time, often presenting extensive suppurative inflammation, while the surface of the brain shows only scattered, smaller inflammatory foci (meningo-encephalitis). Embolic abscesses are found often in pyemia as sharply circumscribed, small, purulent foci, surrounded by greatly dilated vessels, the outer walls of which are infiltrated (Plate 105, Fig. 1). When such purulent accumulations exist for some time, they lead to softening of the nervous tissue about them and to the appearance of contractile cells, as in encephalomalacia. Even large solitary abscesses, such as may result from the entrance of a foreign body or from suppurative sinus thrombosis, may heal spontaneously after the micro-organisms die out. The pus corpuscles are disintegrated from fatty changes, and the margins present the same evidences of connective-tissue ingrowth as older foci of softening. Around the abscess a membrane forms, which becomes firmer and firmer, and at last distinctly fibrous. The encapsulated pus may be inspissated so as to resemble a caseous or chalky mass, and as such it may persist for years.

Virchow designated as *encephalitis neonatorum* a process

PLATE 106.

FIG. 1.—Focus of Softening in Posterior Horn of Spinal Column following Trauma. $\times 54$. 1, Central canal ; 2, softened focus filled with contractile cells.

FIG. 2.—Degeneration in Posterior Columns in Tabes Dorsalis. Marchi preparation with osmic acid. $\times 37$. 1, Septum posterius of spinal cord ; 2, wedge-shaped zone of degeneration in posterior columns ; the degenerating nerves blackened by osmic acid ; 3, adjacent normal spinal tissue.

which probably is not pathologic, but connected with the normal development of the brain. In older fetuses, and in infants up to the seventh month, circumscribed, turbid, yellow foci may be found in the cortex. Microscopic sections show the presence of numerous spindle-shaped and rounded cells, filled with fatty granules. These granular cells are found especially in the lymphatic sheaths of the cortical vessels. At times the ganglion cells also appear turbid and infiltrated with fat granules.

Acute anterior poliomyelitis is the name given a process in the spinal cord, regarded as of inflammatory nature, the territory involved corresponding to the distribution of the arteriæ sulcocommissurales. There is cellular infiltration of vascular sheaths and their vicinity, and degeneration and disintegration of the ganglion cells of the anterior horn. The ganglion cells may perish altogether on one side, or material diminution in number and in size may result.

PLATE 107.

FIG. 1.—Hydromyelia. Weigert myelin sheath stain. $\times 9$. Central canal dilated irregularly and widely. (From upper cervical region.)

FIG. 2.—Tabes Dorsalis. Cervical portion. Weigert's myelin sheath stain. $\times 9$. 1, Degenerated posterior columns ; 2, normal marginal zone.

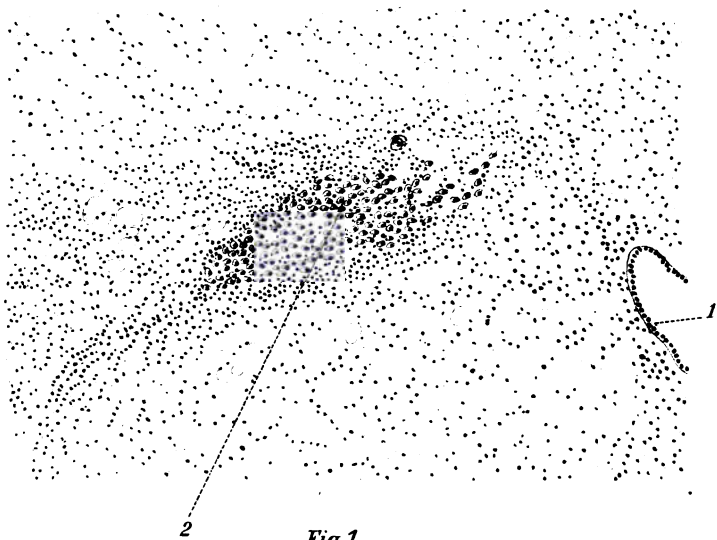


Fig. 1.



Fig. 2.



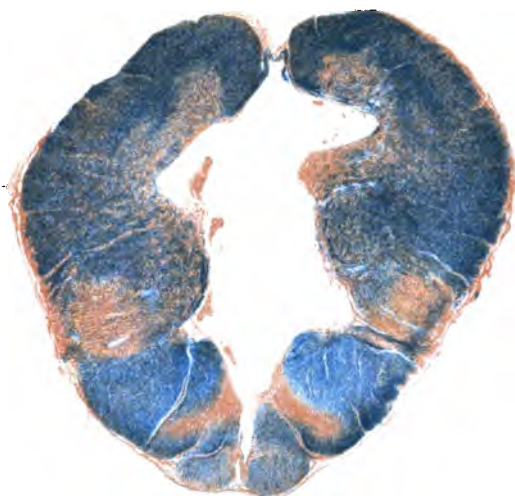


Fig. 1.



Fig. 2.



Sclerotic Processes in the Central Nervous System.

Sclerosis includes numerous histologic processes in the central nervous system, which may differ greatly in their clinical manifestations. Here belong *tabes dorsalis*, the various secondary systemic diseases, which appear after focal or transverse lesions as ascending and descending degenerations of the cord, and the so-called combined system diseases (in amyotrophic lateral sclerosis, spastic spinal paralysis, and progressive paralysis); furthermore, chronic poliomyelitis, numerous cases of syringomyelia and porencephaly, and, finally, multiple cerebrospinal sclerosis.

The common feature of all these diseases is death or destruction of the nerve fibers and proliferation of the glia tissue to cover the defect. In destructions of the central nervous tissue by hemorrhage or as the result of vascular occlusions, repair is accomplished by connective-tissue proliferation, but the purely sclerotic processes are characterized by condensations in the neuroglia, which frequently assume a character like that of genuine neoplasms. And it cannot in all cases be determined definitely whether the primary event of the disease is destruction of the nervous tissue or proliferation of the glia. In the systemic diseases of the spinal cord there occurs in the regions involved first a swelling of single axones or of groups of axones, which on cross-section may present a diameter many times the normal (compare edema of central nervous system, p. 145). This is followed by disintegration of the axones, accompanied by the accumulation in them of fat, and by fragmentation, resorption being the final step in their disappearance. Now numerous myelin sheaths are found empty; between the empty sheaths may be seen occasional normal axones for a long time. But the myelin sheaths also present destructive changes; they are broken up into pieces, and between the fibers appear granule cells, which transport the detritus. A clear picture of this process is given by preparations in which the

PLATE 108.

FIG. 1.—**Marginal Zone of Posterior Columns in Tabes Dorsalis.** Weigert's myelin stain. $\times 67$. 1, Gray substance; 2, marginal zone, the medullary sheaths largely preserved; 3, zone of degeneration.

FIG. 2.—**Marginal Zone of Posterior Columns in Tabes Dorsalis.** Axone stain. $\times 280$. 1, Normal axones; 2, swollen axones; 3, degenerated fibers without axones.

medullary sheaths are colored by Weigert's method (Plate 108, Fig. 1), as well as in specimens stained to bring out the axones (Plate 108, Fig. 2), and in preparations treated with osmic acid according to Marchi's method, which brings out the products of disintegration (Plate 106, Fig. 2). In the first instance one sees, instead of blue rings, only transparent spaces in the condensed but unstained glia tissue. In tabes dorsalis, in which the posterior columns degenerate, there is nearly always a small, relatively normal band immediately adjacent to the gray substance: that is, at the apex of the posterior columns. Here normal myelin sheaths as well as axones may be seen (Plate 108, Fig. 1 (2), and Fig. 2 (2)). The study of specimens prepared by Marchi's method shows most clearly the extent of the area of degeneration, because the myelin

PLATE 109.

FIG. 1.—**Multiple Sclerosis in Spinal Cord.** Weigert's glia stain. $\times 9$. The blue areas consist of condensed glia tissue within which the nervous elements have perished.

FIG. 2.—**Proliferation of Glia in Posterior Columns in Progressive Paralysis (Beginning "Gliosis").** Weigert's glia stain. $\times 300$. The glia network is irregularly condensed; in some places into solid, insular bands (3). 1, Nerve fibers; 2, normal glia tissue.¹

¹ I owe the preparations illustrated on Plate 109 to my deceased friend, Dr. Karl Straub.

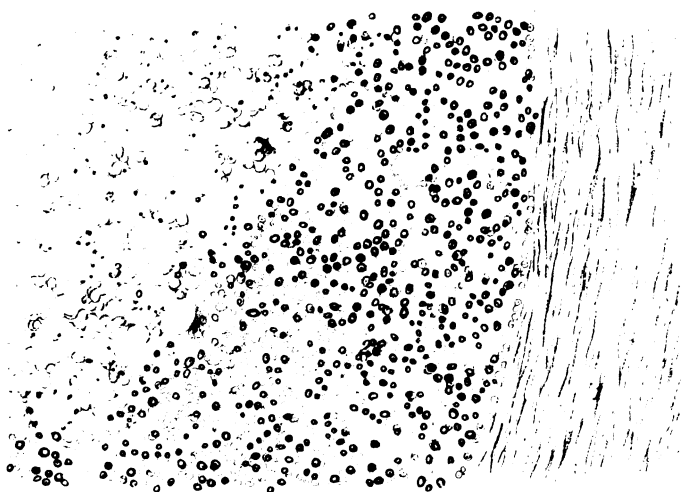


Fig. 1.

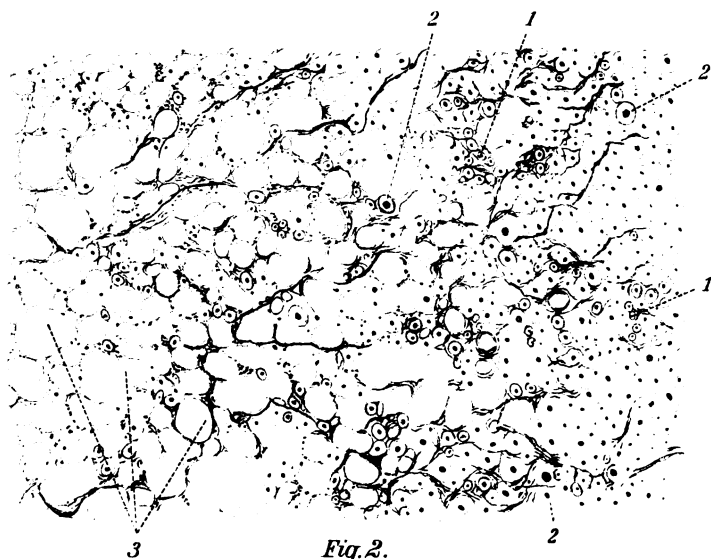
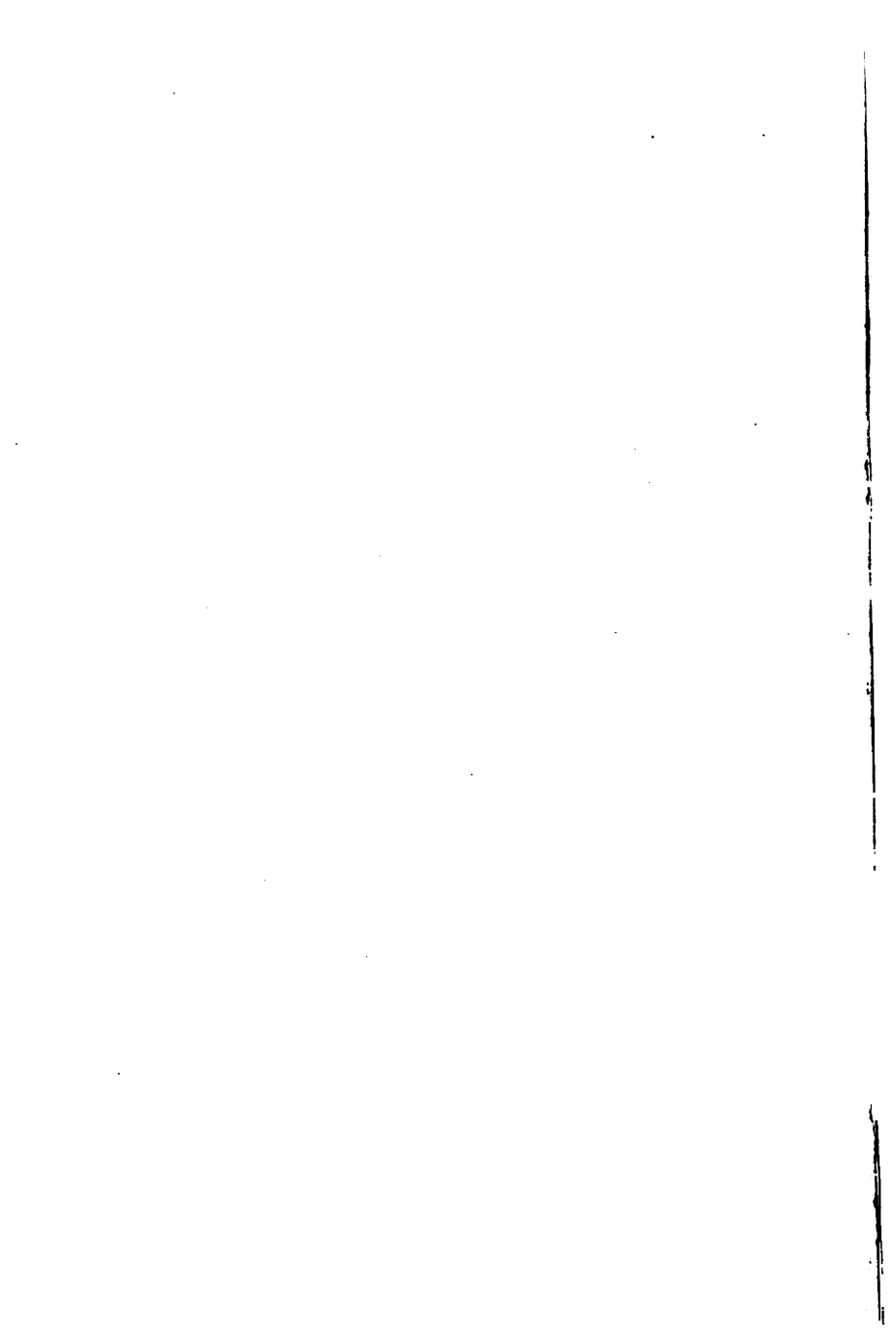


Fig. 2.



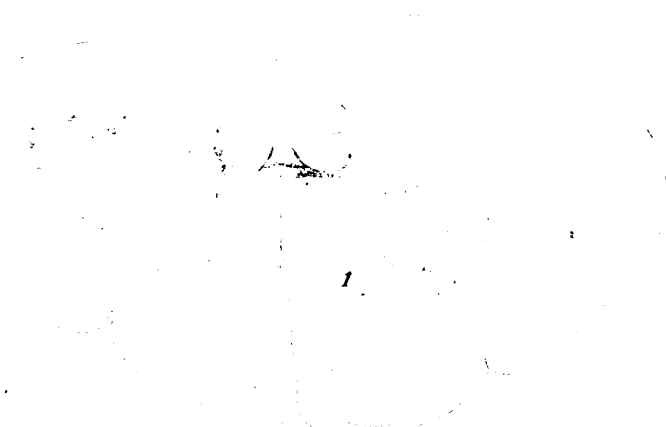


Fig. 1.

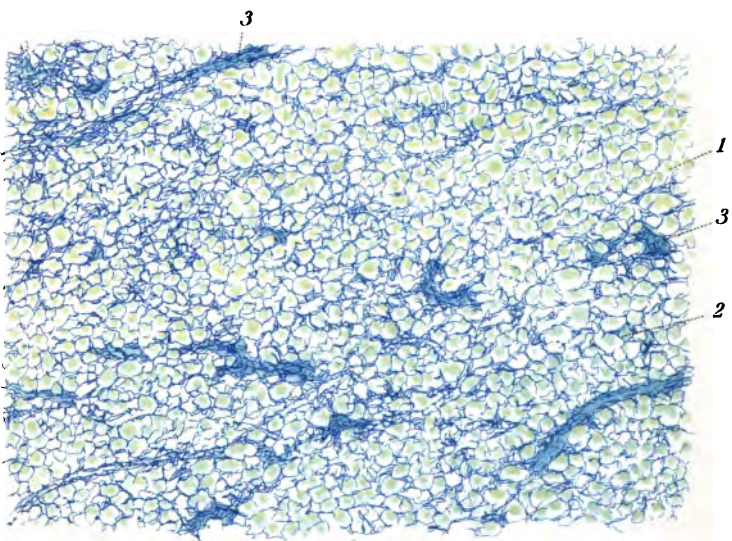


Fig. 2.



sheaths are stained black by osmic acid. As regards the glia, recent specific staining methods, elaborated recently by Weigert [and by Mallory], show best the extent as well as the origin of the sclerotic foci. Under low powers the sclerotic foci appear as circumscribed blue foci (Plate 109, Fig. 1), while with higher powers there is seen a marked increase in glia fibers, which are gathered in dense bundles at the same time as the nerve fibers have perished (Plate 109, Fig. 2). In multiple sclerosis of the brain and cord simple nuclear and protoplasmic stains demonstrate considerable increase and enlargement in the glia cells, which appear swollen, often provided with two nuclei, the cell body giving origin to numerous fibrillæ, and forming thus the so-called spider cells or astrocytes. (Very likely this is an artefact, the fibers not being connected with the cells.)

By syringomyelia is understood dilatation of the central canal of the spinal cord, which often sends out radiating recesses and compresses the substance of the cord. In the vicinity of such cavities there is always considerable proliferation of the glia, often in the form of nodular accumulations. Simpler dilatation of the central canal, without hyperplasia of the glia, is called hydromyelia.

Tuberculosis of the central nervous system is frequently due to extension from the piaarachnoid (tuberculous meningo-encephalitis and meningo-myelitis) (Plate 105, Fig. 2). In addition, there occur also solitary tubercles, especially in the brain, which may vary from minute masses to caseous deposits the size of a goose egg. The microscopic examination shows that it concerns mostly conglomeration of single smaller nodules; hence the name conglomerate tubercle. Outside the caseous zone is usually a wall of round cells, and around the mass is typical softening, recognizable by a wall of large contractile cells loaded with detritus (Plate 105, Fig. 2).

In the same way syphilis of the nervous system results either from direct extension from the meninges (as men-

PLATE 110.

FIG. 1.—**Progressive Muscular Atrophy.** Freshly isolated, unstained fibers. $\times 300$. 1, Atrophic narrow muscle-fibers; 2, normal fiber; 3, fiber filled with fat droplets.

FIG. 2.—**Progressive Muscular Atrophy.** $\times 260$. All muscle fibers much narrowed, transverse striation not recognizable, nuclei proliferated, single narrow fibers changed into so-called muscle tubes (1).

tioned) or as circumscribed guminous foci with caseous centers, mostly encapsulated by sclerotic tissue.

(Concerning tumors of the central nervous system, see "General Pathologic Histology.")

THE SKELETAL MUSCLES.

The voluntary muscles consist entirely of striped fibers. The fibers are long thread-like cells, which vary in thickness from 10 to 100 microns. The cells consist of alternating transverse bands of isotropic and anisotropic substance and of parallel fibrillæ held together in groups by sarcoplasm (Cohnheim's fields). Each fiber is surrounded by a structureless sheath, the sarcolemma, which is again surrounded by a delicate fibrous sheath, the perimysium. The long, oval nuclei of the muscle-fibers of man lie in the sarcoplasm under the sarcolemma.

Degenerations.

Progressive muscular atrophy is an independent affection of the voluntary muscles of unknown etiology. In the early stages the macroscopic changes are very insignificant, the muscle being only somewhat paler and softer than normal. Microscopic sections show a distinct narrowing of many fibers, but the most striking feature is the great increase in muscle nuclei. Later the striated muscle tissue with few, long nuclei is replaced by fibrillar tissue in which transverse striations are recognizable only in a few places. The fibers contain long, vesicular nuclei arranged thickly one after the other; many fibers are converted into so-called

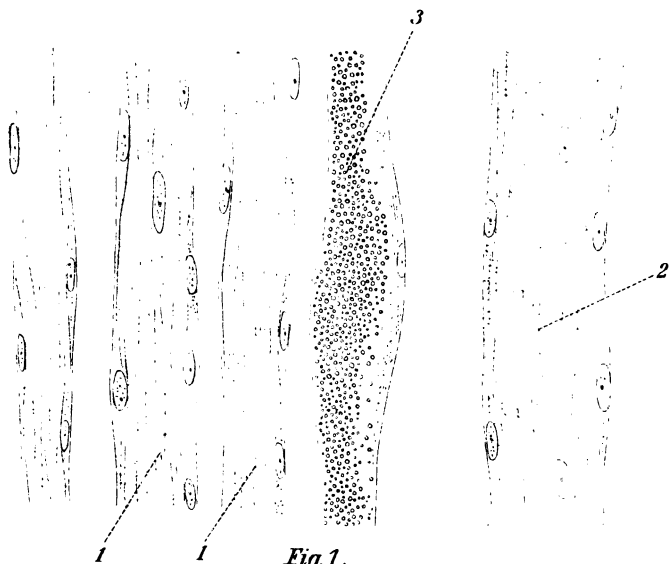


Fig. 1.

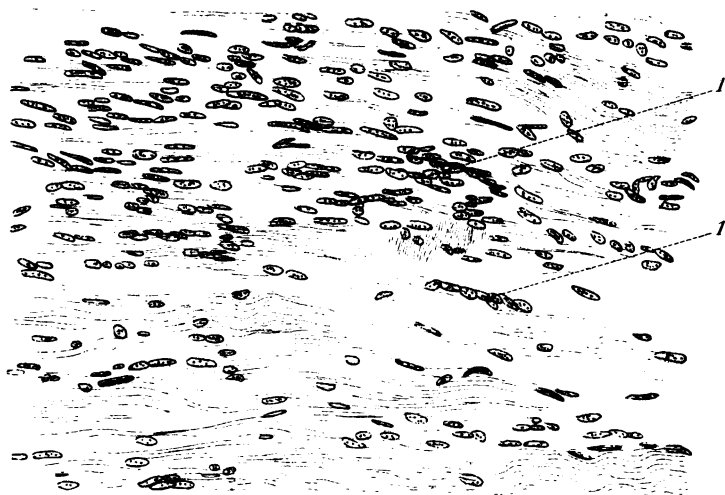


Fig. 2.

"nuclear tubules," in which the nuclei are so numerous that they touch one another (Plate 110, Fig. 2). The distinction between individual cells is no longer clear; in many places the small amount of protoplasm about heaps of nuclei resembles not a little long-drawn-out giant cells. The proliferation of nuclei in muscle-fibers is observed in many retrogressive changes: *e. g.*, in simple atrophy from inactivity, as may be studied in pieces of muscle from the stumps of amputations, and also in muscles that are invaded by tumors. Usually there is at the same time proliferation of the fixed cells in the interstitial tissue,—that is, in the perimysial sheaths,—and the muscle-fibers are pressed apart.

As the real muscle substance disappears more and more, there is formed a richly nucleated, fibrillated connective tissue, which it becomes increasingly difficult and at last impossible to distinguish from the sarcolemma sheaths filled with nuclei. Fresh teased preparations from an early stage show, in addition to narrowing and nuclear proliferation, that occasional fibers are filled full with fat droplets, the transverse striation and the nuclei being lost almost wholly. It is also observed that muscle-fibers disintegrate in a longitudinal direction ("streifige degeneration") as well as in the transverse diameter, forming short segments (the discoid disintegration of Zenker).

In stained sections of muscle at this stage there are seen also vacuoles corresponding to fat droplets.

Frequently degeneration and disintegration are associated with proliferation of fat tissue in the perimysium; the degenerating or still normal fibers then become pressed far apart. Finally, cross-sections show only single islands of muscle bundles, between which is a continuous adipose tissue (Plate 111, Fig. 1). The transverse section of the whole muscle is not diminished, but, on the other hand, increased by this deposition of fat, while the contractile substance in reality is reduced to a minimum (muscular pseudohypertrophy).

PLATE 111.

FIG. 1.—**Pseudohypertrophic Muscle in Cross-section.**
× 78. 1, Cross-section of persistent fibers; 2, between the muscle-fibers and bundles proliferated fat tissue; 3, disintegrating fibers filled with fat vacuoles.

FIG. 2.—**Hyaline Degeneration of Striated Muscle-fibers in Amputation Stump of Thigh.** × 70. 1, Normal fibers; 2, hyaline bands and flakes.

A waxy or hyaline degeneration of muscle occurs in certain infectious diseases, especially in typhoid fever, and also in smallpox, chronic tuberculosis, and trichinosis. In typhoid fever the recti abdominis and adductores femoris are the muscles involved especially.

The single muscle-fibers are swollen, and appear in fresh specimens as very light, peculiarly glistening bands (Plate 111, Fig. 2); then a granular appearance develops, the transverse striations disappear, and the fibers change into strongly refractile scales, which seem to be exceedingly fragile. Longitudinal splits and irregular transverse fractures occur. Thus may be produced larger tears in the muscles, accompanied with rupture of larger blood-vessels and extensive hemorrhages (muscular apoplexy), as illustrated by the hematoma of the recti abdominalis in typhoid fever [and occasionally in other diseases].

Fatty degeneration of the skeletal muscles occurs in many infectious diseases and intoxications, especially phosphorus- and arsenic-poisoning. Its course is similar to that of fatty degeneration of the myocardium (Vol. I, p. 20).

Amyloid degeneration of the skeletal muscles is rare, and occurs only in extensive general amyloidosis. As elsewhere in the body, it starts in the blood-vessels and extends thence to the perimysium and the sarcolemma. The muscular fibers undergo a secondary atrophy. In the tongue large nodular accumulations of amyloid material may occur.

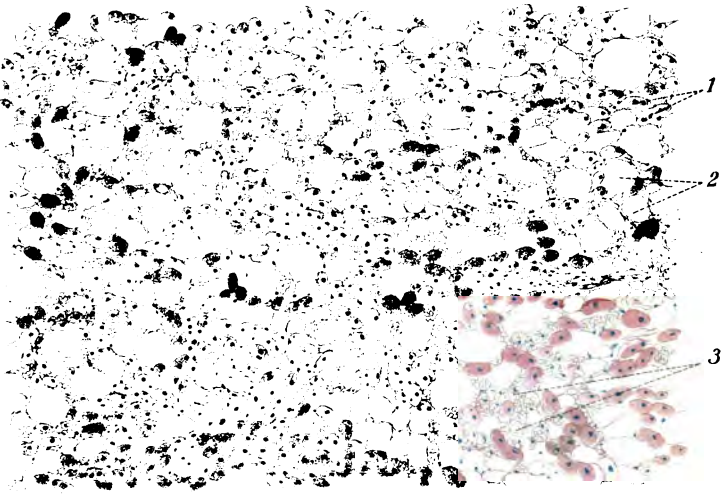


Fig. 1.

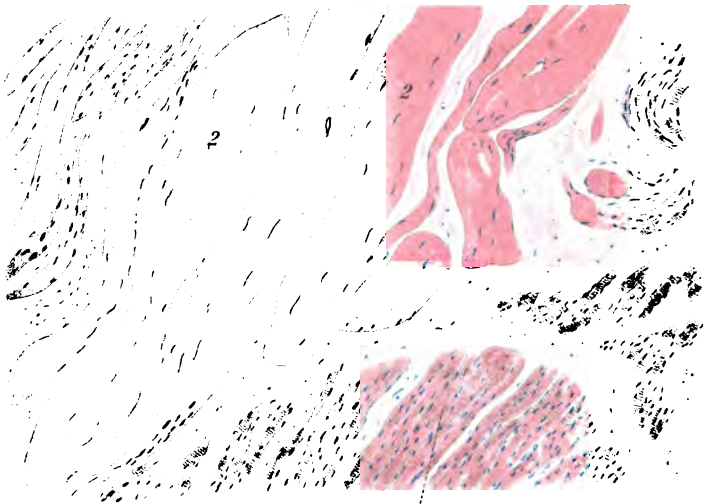
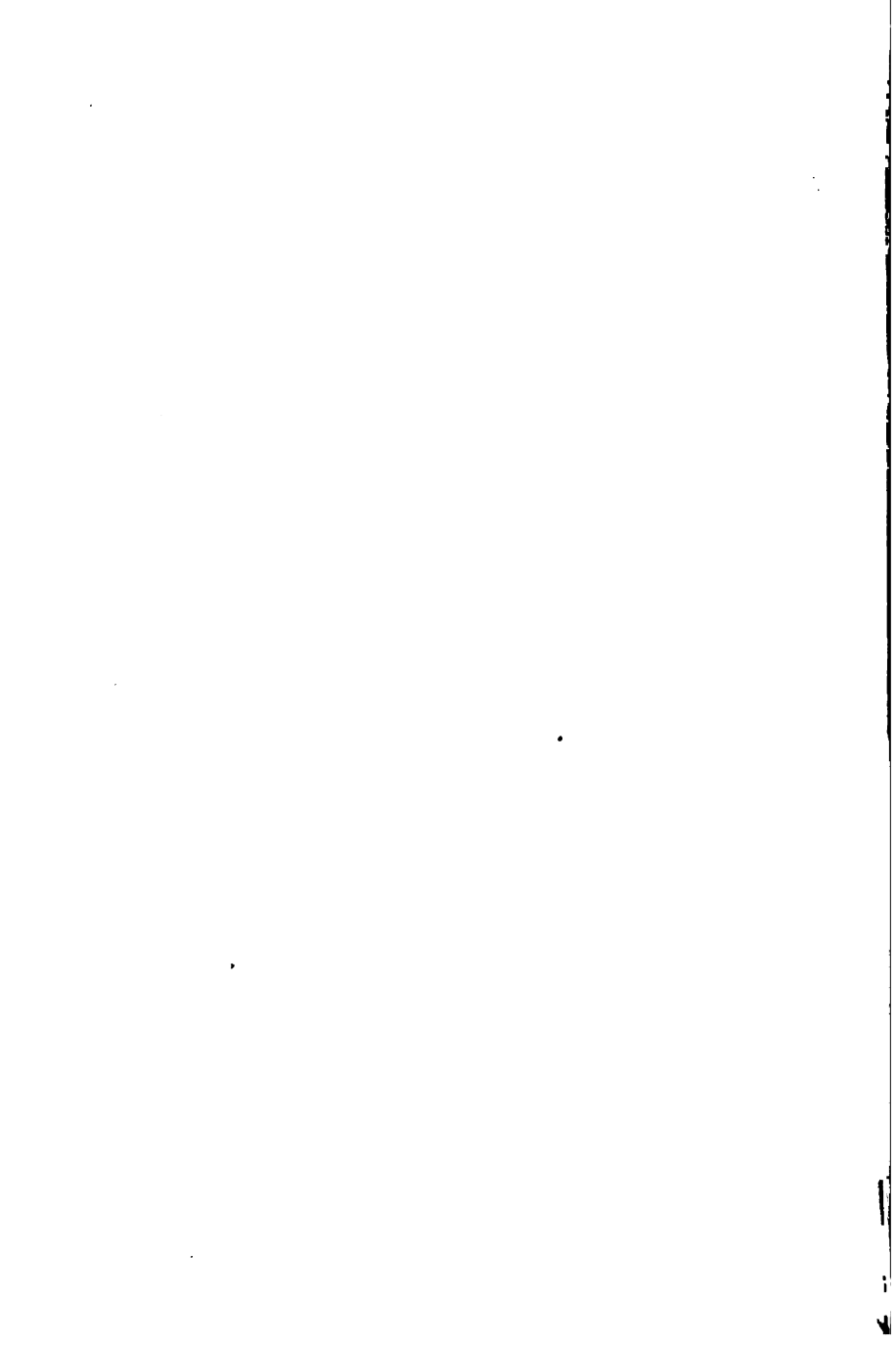


Fig. 2.



Inflammations of Muscles.

Suppurative myositis may arise from extension or embolism; it does not require special histologic description. About parasites there frequently develop accumulations of round cells in the interstitial tissue, especially in trichinosis, as well as about the Miescher's tubules (see "General Pathologic Histology"). [Large accumulations of eosinophile cells are found in muscles recently invaded by *Trichinella spiralis*.—Brown.]

Chronic interstitial inflammations are characterized by proliferation of internal perimysium, and lead to fibrous scars and general connective-tissue substitution of the contractile substance, which slowly undergoes degenerative changes (myositis fibrosa productiva). Frequently ossification of the connective tissue occurs, either locally, as in the so-called rider's bone, or, more generally, throughout whole groups of muscles (myositis ossificans).

Tuberculosis of the muscles originates either by extension from cold abscesses, as in the ilio-psoas muscle and from lymphatic glands, or, more rarely, in general miliary tuberculosis by embolism. Here may be traced readily the transformation into multinuclear giant cells of single segments of the disintegrating muscles, which are infiltrated with numerous nuclei.

THE SKIN.

The Skin.—The skin consists of epidermis or cuticle and corium. The corium consists of interlacing connective-tissue bundles mixed with fine elastic fibers. Two superimposed layers are distinguishable: namely, the stratum papillare, the upper layer, and the stratum reticulare, the under layer. The stratum papillare forms conical elevations or papillæ, which push the epidermis before them. These papillæ carry the finer branches of the vessels and nerves as well as certain nervous end-organs. The corium also contains the cutaneous glands and the roots of the hairs. In the deeper layers of the stratum reticulare occur fat cells, which in many parts form a continuous fatty

PLATE 112.

FIG. 1.—**Pigmentation of the Skin in Addison's Disease.**
 × 70. 1, Stratum corneum ; 2, rete Malpighii ; 3, basal layer greatly pigmented.

FIG. 2.—**The Skin in Vitiligo.** The margin of a vitiliginous spot. × 250. 1, Stratum corneum ; 2, rete Malpighii ; 3, basal layer of epithelium normally pigmented up to 4, at which point there is sudden discontinuance of pigment.

tissue—the panniculus adiposus. The epidermis, which covers all the papillæ and elevations of the corium, contains two principal layers of cells—the stratum Malpighii, or stratum germinativum, and the horny layer, or stratum corneum. The stratum Malpighii shows a basal layer of cylindrical epithelial cells with oval nuclei; then a middle layer of several strata of polygonal cells, the surfaces of which are joined together by short processes or intercellular bridges. Hence these cells are known as prickle cells. The upper layers consist of gradually flattening cells containing numerous granules, which stain deeply with hematoxylin, the so-called keratohyaline granules. These granules form eleidin, a homogeneous substance, which gives to the succeeding cell layers a transparent appearance, on account of which they are known as the stratum lucidum. From the drying of the eleidin the surface of the stratum corneum becomes covered with flattened and horny cells, which are continuously desquamated, to be replaced by other cells from below. Even in the white races the epidermis contains more or less pigment, which in some places—*e. g.*, the scrotum and about the anus—is more concentrated. The pigment is found especially in the basal layers of the stratum germinativum.

The cutaneous glands are : (1) The sebaceous glands. They lie in the superficial layers of the corium, the stratum papillare, and are alveolar glands which generally are closely connected with the hair follicles, their ducts usually emptying into the upper third of the hair follicle. The glandular cells are cubical in the external parts; in the centrally placed strata the cells have a reticular appearance, due to the presence of fat droplets. (2) The sweat glands or coil glands. They lie in the deeper layers of the corium, the stratum reticulare, and are tubular glands, the lower ends of which are coiled up. The cells are cubical, situated upon a basement membrane, and contain small granules of fat and pigment. The ducts run straight through the corium, the course through the epidermis being spiral.

Of the diseases of the skin, naturally only those will be discussed, which have considerable interest anatomically and which are met with somewhat frequently at the autopsy table.

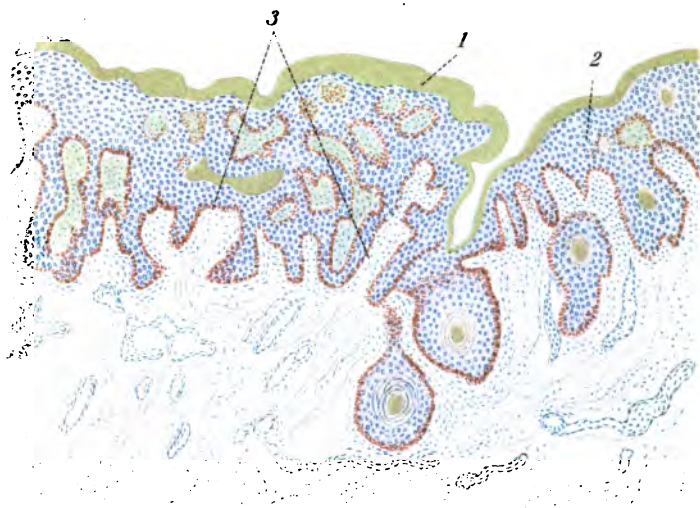


Fig. 1.

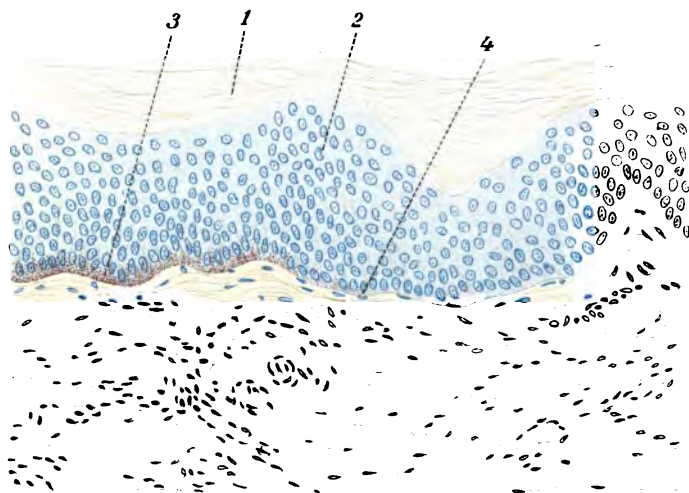


Fig. 2.

Anomalies of Pigmentation.

Increased pigmentation occurs either in circumscribed spots or diffusely. Congenitally marked pigmentation may occur not only in the epidermis, but also in the connective tissue of the cutis; in the latter case more particularly as the so-called moles (birth-marks) or pigmented nevi (Plate 113, Fig. 1). These are often associated with a hyperplasia of the papillary body whereby arise the pigmented warts or papillomas of the skin. Later in life abnormal pigmentations appear, as the so-called lentigines or as freckles or ephelides. A somewhat lighter pigment is seen in xanthelasma or xanthoma and in the spots of chloasma.

The latter appear in women during pregnancy, especially in the face (chloasma uterinum) or in greatly weakened and marantic persons (chloasma cachecticorum). A diffuse pathologic pigmentation of the skin is caused by melasma suprarenale, which, with tuberculosis of the adrenals, constitute the symptom-complex of Addison's disease. Fine, angular pigment granules are found in continuous and dense rows in the basal layer and in the lower layers of the stratum Malpighii of the epidermis (Plate 112, Fig. 1). The pigment is the so-called melanin, which is assumed to be a proteid product containing sulphur.

Abnormal lack of pigment may occur as a congenital anomaly (albinismus), or the pigment disappears from various larger and smaller areas of skin later in life, as under the influence of nervous conditions (leukopathia). A local disappearance of pigment in spots is known as vitiligo. The microscopic examination of the spots of vitiligo show at the margin that the pigmentation of the basal layers of the epidermis ceases suddenly (Plate 112, Fig. 2).

Inflammations of the Skin.

The inflammations of the skin pursue different courses, depending upon the nature of the microbic cause and upon

PLATE 113.

FIG. 1.—**Nævus Pigmentosus.** $\times 70$. 1, Stratum corneum ; 2, rete Malpighii elevated by a high papillary body ; 3, concentric epithelial pearls with hornified cells in the center ; 4, pigment deposits.

FIG. 2.—**Molluscum Contagiosum of the Skin of Dorsum of Foot.** $\times 260$. 1, Stratum corneum ; 2, rete Malpighii ; 3, molluscum bodies ; 4, center of papilla filled with molluscum bodies ; 5, keratohyaline granules.

the seat of the process. The most frequent form, the staphylococcus infections, usually start from the cutaneous glands, more frequently from the sebaceous glands of the follicles, more rarely from the sweat glands. Study of the earliest steps in the process shows masses of staphylococci between and within the gland cells ; and ducts, as well as the sheaths of the hair-roots, contain micro-organisms. The cocci become surrounded by a dense wall of leukocytes, which accumulate more and more, and the gland cells and the membrana propria are destroyed. The dense accumulation of pus corpuscles extends into the adjacent cutis, the collagenous and elastic fibers are dissolved, and there is formed a small cavity filled with pus—a cutaneous abscess.

The papillary body of the corium is flattened, often entirely absent ; the epidermis is compressed, tense, and bulging. When the process involves only a single gland, it is designated as folliculitis ; but when larger areas of tissue are infiltrated with pus and softened, then the condition is known as furuncle.

The increasing accumulation of pus cells and the increasing tension of the walls finally lead to rupture of the abscess upon the surface, and the pus is evacuated spontaneously. The resulting scar in the cutis usually permanently destroys the cutaneous glands and the papillary body, and the new epidermis from the margins spreads itself over a smooth surface of corium.

Erysipelas is a diffuse inflammation of the skin caused

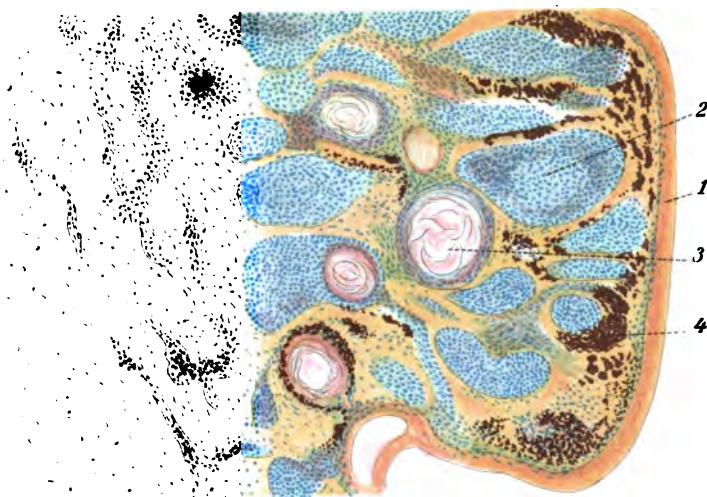


Fig.1.

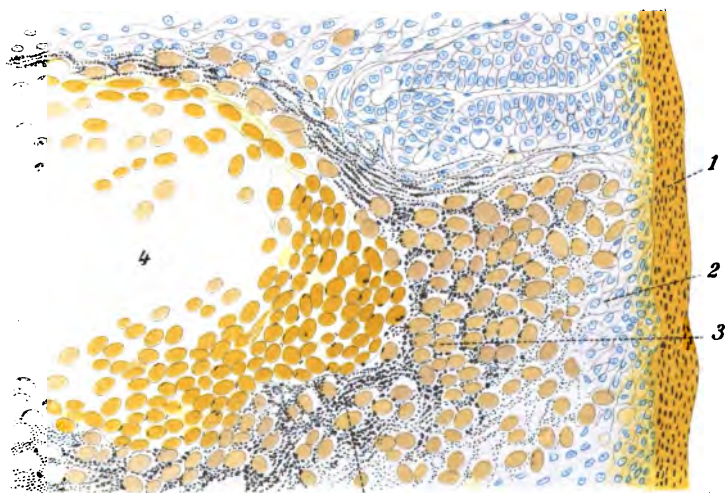


Fig.2. 5

by streptococci and starting in the cutaneous lymphatic channels. The vessels of the cutis and of the subcutaneous tissue become greatly dilated; in the smaller veins and capillaries complete stasis of the red cells may result, and also fibrin formation, as well as desquamation of the lining cells. The cutis and subcutaneous tissue are infiltrated with leukocytes, and the adventitial tissue of the vessels is filled with lines of pus corpuscles. Round cells may accumulate in groups in the septa between the fatty masses of the panniculus adiposus. Especially noteworthy is the dilatation of the lymphatic vessels between the connective-tissue fibers of the cutis; and frequently they seem to be injected, as it were, with accumulations of streptococci. After a few days the cellular accumulations disappear; in their place arise rounded cavities filled with albuminous fluid and cocci in chains, and a marked edematous infiltration of all the layers of the skin results. It is rather rare that extensive coagulation takes place in the dilated lymph spaces. The papillary body becomes flattened over large areas, and the exudation extends to the epidermis also and presses the epithelial cells apart or elevates continuous lamellæ of the various layers. The stratum corneum especially may be raised up into blisters by large accumulations of fluid (erysipelas [vesiculosum et] bullosum). In this form the other cell layers become necrotic, or at least greatly swollen from dropsical accumulations, and even hair follicles and ducts of sebaceous glands may be destroyed. The hairs may be loosened from the sheaths and there may be extensive falling out of hair after erysipelas (Plate 116, Fig. 1).

When suppurative inflammations extend to the subcutaneous tissue and lead to extensive diffuse infiltrations, with simultaneous softening of the tissue, the process is designated as phlegmon. These suppurations are also nearly always caused by streptococci, while the staphylococcus suppurations generally tend to become circumscribed. The subcutaneous tissue first becomes swollen

PLATE 114.

FIG. 1.—Lupus Hypertrophicus of the Skin of Forearm. $\times 22$. 1, Stratum corneum; 2, rete Malpighii; 3, infiltration and giant cells in papillary body.

FIG. 2.—Lupus of Skin of Temple. Gram's stain. $\times 35$. 1, Proliferated epithelium with numerous hornified flakes (2); 3, giant cells in infiltrated papillary body; horny masses in some of the giant cells.

from the exudation of serous fluid into its spaces, which also contain numerous micro-organisms. The blood-vessels in such areas are often thrombosed. Gradually the serous exudation gives way to a purulent infiltration, which is not confined to any one point, but spreads diffusely and leads to extensive softening of the tissue. Often the upper layers of the corium, including the epidermis, are lifted from the subcutaneous tissue. The larger veins are often the seat of a thrombophlebitis and complete softening of the walls (Plate 116, Fig. 2).

In the acute exanthematous diseases also inflammations develop in the skin. Manifestly it concerns the localization of a virus circulating in the blood. The most striking changes from the histologic standpoint are seen in variola. In the first stage there is a marked serous exudation into the stratum Malpighii at the same time as there is marked hyperemia and edema of the papillary body. This causes a prominence of the affected area, and the smallpox pustule develops. Before long a few cells or groups of cells in the center of the exudation into the epidermis undergo necrosis; this causes a slight depression of the dome of the pustule—the central umbilication which is so characteristic for smallpox (Plate 115, Fig. 2). Numerous leukocytes migrate into the papillary body and the lower layer of the epidermis; the exudation and the necrosis of the rete Malpighii continue, leading to complete solution of the cells in the stratum germinativum. This leads to the formation of a cavity filled with clear fluid at first.

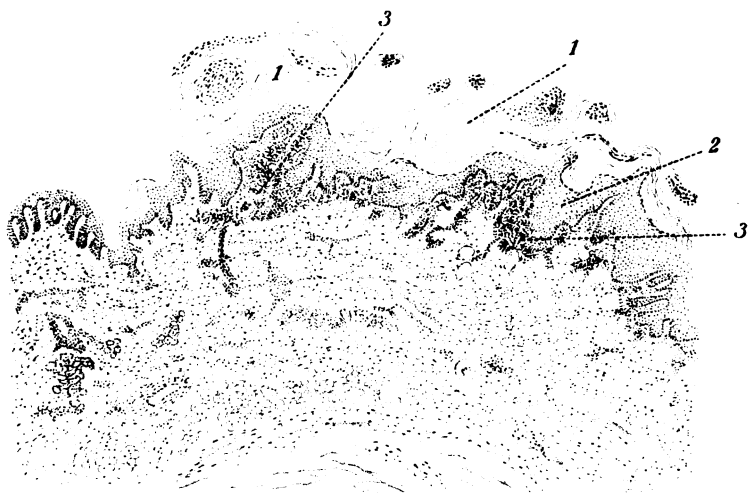


Fig. 1.

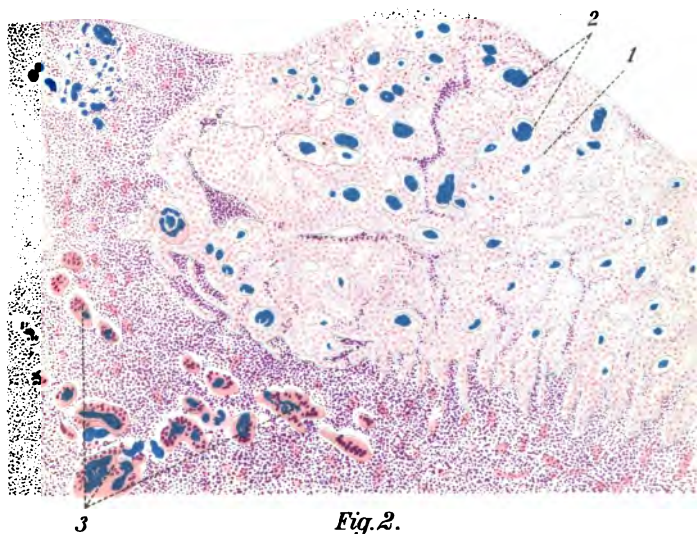


Fig. 2.

The persistence of a few compressed epithelial cells and of remnants of cells may so subdivide the cavity as to give it a characteristic spongy appearance. At this time the smallpox pustule is at the height of its development (stadium floritionis). Gradually the fluid is rendered turbid by the entrance of leukocytes with fragmented nuclei. The dividing walls of the cavity are broken through, the intravesicular pressure becomes greater and greater, and the umbilication of the pustule may be elevated and smoothed out (variola globosa). At last the superficial layers of the stratum corneum rupture, giving the pus free exit, and the pustule empties itself (stadium suppurationis). The drying of the pus upon the exposed surface covers the ulcer with a crust (stadium exsiccationis). Epithelial cells at the margins grow in under the crust, which is gradually loosened at the same time as the defect is covered. When the suppuration has extended into the papillary body and led to softening in the upper layers of the corium, connective-tissue proliferation and scar formation result, and since the papillæ are not replaced at all, or only imperfectly, there results the smallpox scarring or pitting, of small rounded areas or of depressions traversed by a network of small ridges. The pigment is nearly always lost in these scars.

A special form of smallpox is the so-called black smallpox, or variola hæmorrhagica. The pustule develops according to the type described, but the contents consist of blood instead of serous fluid. The escape of the red blood corpuscles does not seem to depend upon severe vascular lesions and ruptures, because injected preparations do not show the injected mass in the pustules. The blood corpuscles evidently pass out from the surrounding vessels as the result of diapedesis. Real suppuration also develops in the hemorrhagic form, for there is a marked infiltration of the papillary body and the surrounding layers of the corium; but on account of the early death of the patient, a typical suppurative stage is not reached.

PLATE 115.

FIG. 1.—Anatomic Tubercle of Finger. $\times 55$. 1, Stratum corneum; 2, granules of keratohyalin in superficial epithelium; 3, rete Malpighii; 4, greatly elongated papilla; 5, tubercles in papillary layer with numerous giant cells.

FIG. 2.—Variolous Pustule in Skin of Back. 1, Stratum corneum; 2, rete Malpighii; 3, rete Malpighii transformed into a spongy network the spaces of which contain a few round cells. In the cutis cross-sections of hair follicles.

Anthrax infection of the skin leads to histologic changes quite similar to those of variola—the so-called pustula maligna. The bacilli enter through the epidermis, either by way of small injuries or, as in furuncle, through the ducts of the sebaceous glands and the hair follicles. There is early great increase on the part of the bacilli, which invade the adjacent tissue, especially the corresponding papillary body. The papillæ and the corium are rendered highly congested, densely infiltrated with pus corpuscles, and masses of bacilli appear in the vessels of the papillæ and their vicinity. The suppuration extends downward into the subcutaneous tissue, and here the process assumes a phlegmonous type. The papillary bodies are flattened, the epidermis is made tense, and the invasion with anthrax bacilli and infiltration with leukocytes cause spots of necrosis in the epidermis, through which the pus may escape. As in variola, the stratum Malpighii may show circumscribed cavities in consequence of local mortification of prickle cells and serous exudation.

Pemphigus is another disease characterized by early serous exudation into the epidermis, and later by the accumulation of pus, which leads to the detachment and elevation of layers of the skin. If large pustules form, the disease is designated as pemphigus foliaceus.

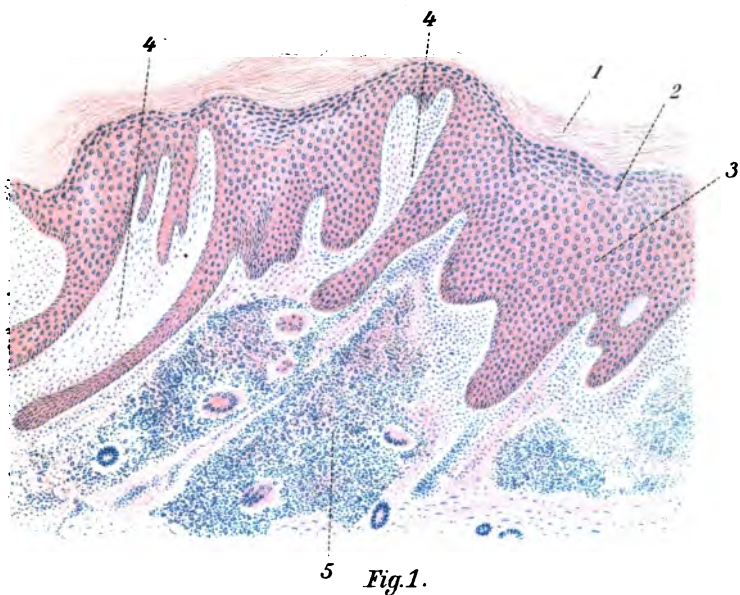


Fig. 1.

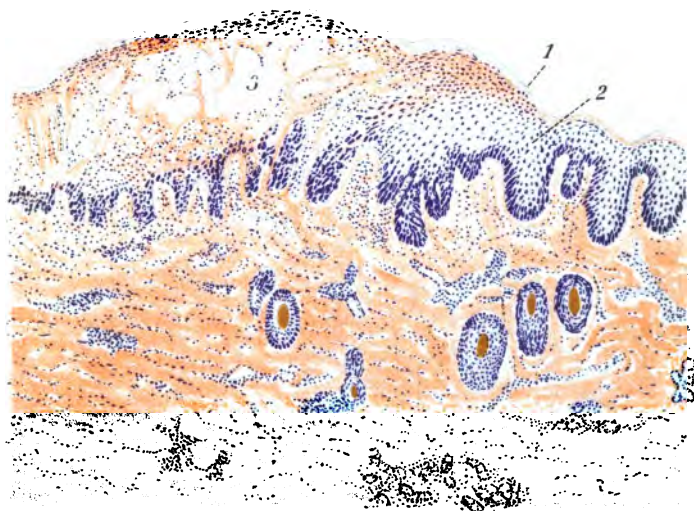
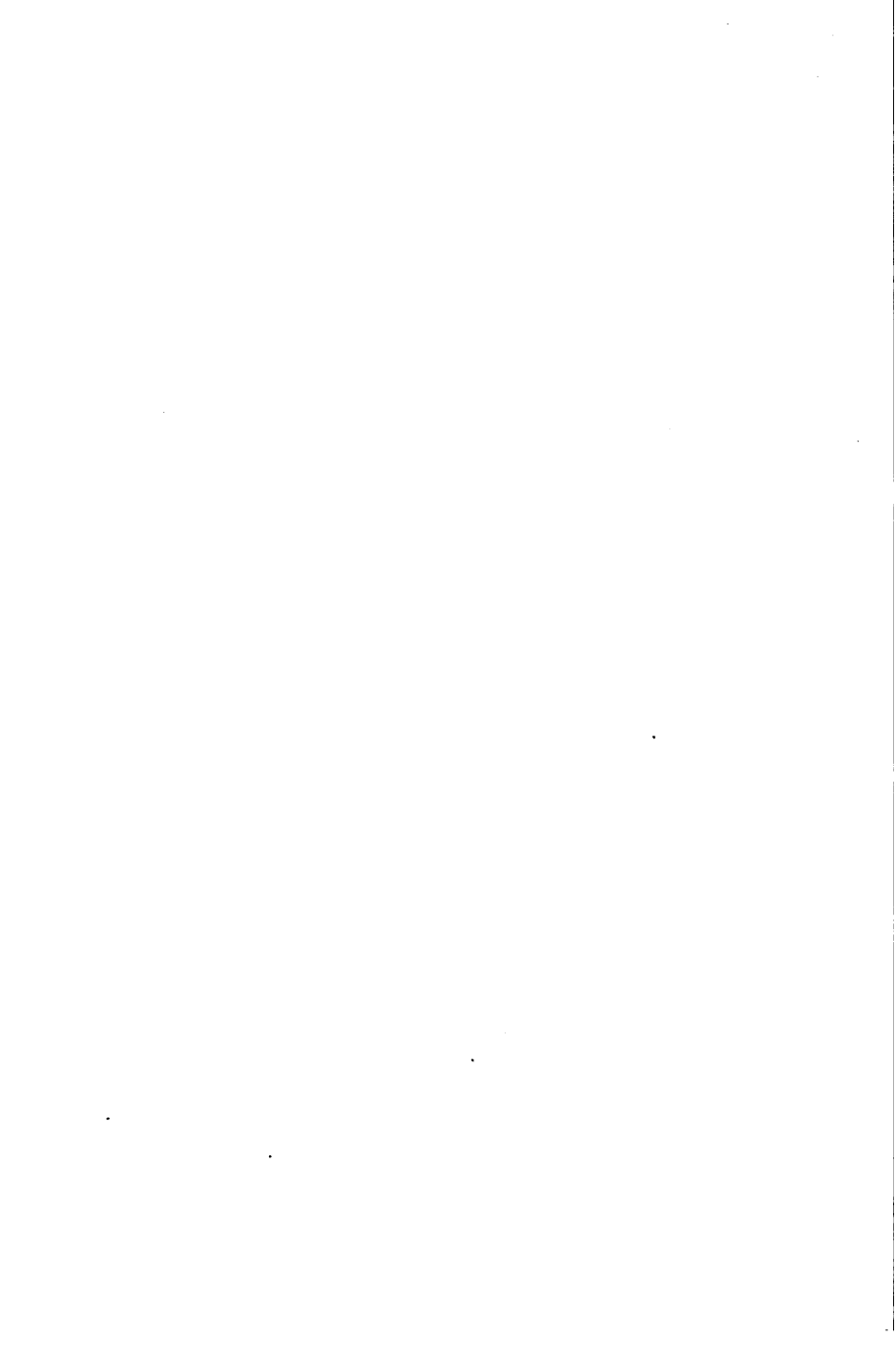


Fig. 2.



Tuberculosis.

Tuberculosis of the skin occurs either as circumscribed nodules in the upper layers of the papillary body, associated with hyperplasia of the latter, which gives rise to warty outgrowths (*tuberculosis verrucosa cutis*), or in the form of diffuse infiltration of the corium, often associated with atypical proliferation of the epithelium of the epidermis (*lupus*).

Anatomic tubercle (postmortem wart) is a circumscribed tuberculous nodule in the skin caused by a direct inoculation of tubercle bacilli. The upper layers of the corium are the seat of small nodules of epithelioid and giant cells surrounded by round-cell infiltration reaching into the papillary body (Plate 115, Fig. 1). The nodules contain tubercle bacilli, demonstrable microscopically and by means of animal inoculations. At the same time the papillæ become extraordinarily long and tall; the interpapillary epithelial processes seem long-drawn-out and extend deeply into the skin. Often the surface of the wart-like growth shows fissures in the epithelium (*tuberculosis verrucosa cutis*). Occasionally suppuration takes place, evidently due to simultaneous or secondary mixed infection with pus microbes. The nodules often disappear spontaneously.

Lupus, the second form of cutaneous tuberculosis, is characterized also by the eruption of typical tuberculous nodules; but these are not limited to a small place in the skin, but scattered over larger areas. The tubercles are situated primarily in the papillary body, and consist of epithelioid and giant cells surrounded by round cells. Tubercle bacilli are usually very sparse. Between the tubercles there is frequently a diffuse granulation tissue throughout the corium, which becomes thick and broadened, so as to rise above the level of the surrounding skin (*lupus hypertrophicus*). The epithelium always participates; it may be the seat of ulcers caused by the enlargement of the nodules which rupture externally (*lupus*

PLATE 116.

FIG. 1.—Erysipelas of the Skin. $\times 100$. Stratum corneum desquamated and wholly absent. 1, Stratum Malpighii; 2, accumulation of streptococci between the cells of rete; 4, streptococci in cutis; 3, cutis with groups of leukocytes and rounded spaces filled with edematous fluid.

FIG. 2.—Phlegmon of Subcutaneous Tissue. $\times 60$. 1, Subcutaneous fat infiltrated with cells; vessels greatly congested; 2, adventitia of a large thrombotic vein; 3, slit-shaped remnant of lumen of vein; 4, media infiltrated with leukocytes.

exulcerans), but that is more rare. Usually the nodules appear to stimulate the epithelium to increased cellular activity, which leads to increased thickness of the rete Malpighii, and especially to a proliferation of the cells of the stratum granulosum, which consists of numerous layers of large polygonal cells covered by a horny layer, many times thicker than normal, the surface being the seat of extensive desquamation (lupus exfoliativus—Plate 114, Fig. 1). In many places the interpapillary epithelial processes send downward long, branching outgrowths, and the sections show numerous epidermal islands, in which increased transformation of keratohyalin into eleidin leads to formation of much horny material. In this way the deeper layers of the granulation tissue may come to contain extensive, concentrically lamellated, centrally hornified epithelial masses. This atypical epithelial proliferation must be carefully distinguished from carcinoma (see "General Pathologic Histology," "Tumors"). When hornified masses from the epithelial proliferations become scattered in the granulation tissue, they may be incorporated by phagocytic cells, and multinuclear giant cells may develop around the horny material, which acts as a foreign body ("foreign body giant cells"). The cells are easily distinguished from tuberculous giant cells (Plate 114, Fig. 2). Especially instructive pictures are obtained by means of Gram's stain, which colors the horny material blue.

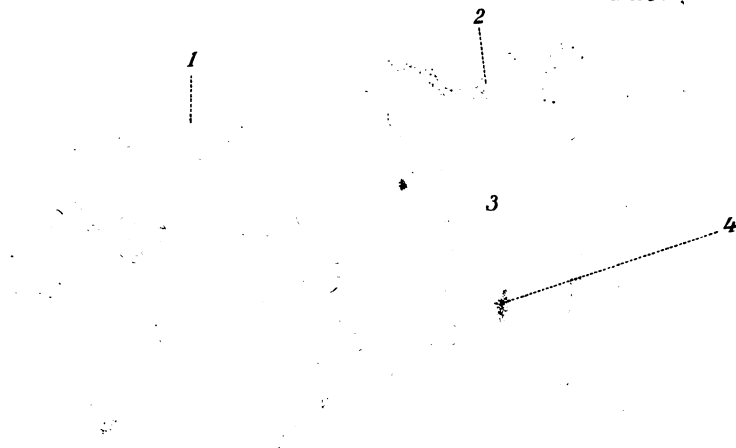


Fig. 1.

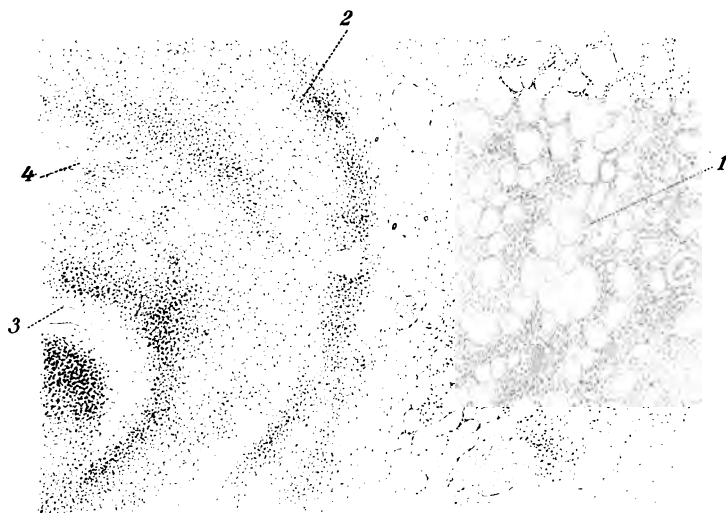


Fig. 2.

Syphilis of the Skin.

In the primary stage of syphilis the cutaneous lesion consists in the initial sclerosis or hard chancre. A small, wart-like, hard growth appears. Usually the epidermis is wholly intact, the corium and the papillary body show a diffuse infiltration with small cells of the nature of lymphocytes, and the connective-tissue fibers of the corium are thick and stiff, often amalgamated into hyaline layers, resembling the ground substance of cartilage. The vessels frequently show specific changes, all the layers of the walls being infiltrated with round cells, the epithelium of the intima greatly proliferated, so that much narrowing, and even complete closure, may result.

In the tertiary stage of lues, gummous formations, starting in the connective tissue of the cutis, may develop in the skin. The center often disintegrates into a fatty or mucoid material, leading to softening, rupture, and ulcerating surfaces (serpiginous ulcers).

Leprosy.

Leprosy causes characteristic changes in the skin concerning which a few statements may be made. Microscopic sections usually show that young lepra nodules are covered with an intact epidermis. The papillæ are cellular, in part enlarged, and often obliterated; in the vicinity of the sweat glands, and especially of the vessels and nerves, is a dense infiltration of small round cells. Many of the larger arteries and veins of the tissue of the cutis are obliterated wholly. Dense cellular accumulations take place around the Pacinian corpuscles within the limits of the leprous nodule. The leprous infiltrations are formed mostly by small round cells, and the margins are usually ill defined; toward the center of the nodule the cells become larger; downward, the infiltration, following the connective-tissue bands and the vessels, may reach to the panniculus adiposus; and laterally the nodules, without

sharp limits, pass into normal tissue. Leprosy nodules frequently contain multinuclear cells, which probably arise from the fixed tissue cells and from the vascular epithelium.

The nodules contain the well-known heaps and masses of acid-proof leprosy bacilli ; these are often intracellular. Later proliferation of the connective-tissue elements of the corium causes extensive cicatricial induration of the skin, and, as in lupus, these areas may present typical epithelial hyperplasia.

Molluscum Contagiosum.

Molluscum contagiosum, or epithelioma contagiosum, is a disease of the skin which seems to result from a parasitic invasion of coccidia. Small warty growths are formed, with a central depression. The whole growths consist of proliferated prickle cells, which form gland-like or pouch-like downgrowths. In the center of the upper part of the proliferation are found the oval, egg-like molluscum bodies, which are regarded by some as parasites, but by others as degenerated and colloid epithelial cells. In the surrounding layers of the epithelium, and also between them, are masses of opaque, angular granules of keratohyalin.

[Blastomycetic Dermatitis.

This is an interesting chronic inflammatory process in the skin caused by organisms belonging to blastomycetes and oidia. Their botanical position has not yet been determined. The clinical features of the disease recall now tuberculosis, now syphilis, now carcinoma. The histologic changes consist of epithelial hyperplasia, infiltration of embryonal cells, plasma cells, leukocytes, and lymphocytes. Giant cells of the tuberculous type are frequent. A characteristic feature is the formation of small miliary abscesses, often intraepithelial, in which the organisms occur more constantly than elsewhere as double-contoured, budding, spherical masses.]

THE BONES AND JOINTS.

THE BONES.

The bones consist of ground substance and of bone cells. The ground substance is made up of fibrillæ, held together by cement, and made hard and dense by impregnation with calcareous salts. In the ground substance are numerous oval cavities connected with one another by exceedingly minute canals. The cavities contain the bone cells, which send protoplasmic processes into the canals. Bone is formed by calcification of a membranous or cartilaginous ground substance. The bone cells arise from osteoblasts which lie at the side of the ground substance and gradually become inclosed by it during the process of calcification. The ground substance of compact bone is furthermore traversed by a system of large canals and spaces, which contain the nutritive vessels and are called Haversian canals. The bone substance is arranged as concentric Haversian lamellæ around these canals. The articular ends of bones are covered by a layer of hyaline cartilage of varying thickness. The fibrous capsules of joints have a glistening internal lining—the stratum synoviale, or synovial membrane. From it project into the joint small villous processes of vascular and fatty connective tissue. The synovial membrane is covered internally with many layers of flat epithelial cells.

Rickets.

The histologic changes in rickets are quite complicated, and they are made clear only by keeping distinct from one another the various processes that enter into play. These processes are :

1. Absence or defect in the calcification of newly formed bone tissue.
2. Abnormal persistence of non-calcified "osteoid" tissue.
3. Proliferative processes in cartilage, periosteum, and bone marrow.
4. Increased absorption of fully formed bone substance.

In the diaphyses of the long bones rickets shows itself especially by absence of calcification. Ground substance is formed as in normal ossification, both periosteal and endochondral, but there are marked deviations from the normal structure, in that the arrangement of the Haversian

PLATE 117.

FIG. 1.—**Rickets in Epiphysis of Rib.** $\times 20$. 1, Resting, hyaline cartilage, containing a few sprouts from the marrow; 2, large-celled cartilage arranged into irregular groups; 3, lateral protuberance of zone of proliferation; 4, sprouts from marrow penetrating into cartilage; 5, displaced trabeculae of osteoid tissue; 6, bone of periosteal origin.

FIG. 2.—**Rickets in Epiphysis of Rib.** $\times 90$. Details from preceding figure. 1, 2, Large-celled cartilage, the cells arranged in groups and rows; 3, trabeculae of spongy bone covered with osteoid tissue; 4, sprouts from marrow penetrating cartilage; 5, osteoclasts.

lamellae is not regular, there being either too many layers or an atypical interlacing. The trabeculae formed by the periosteum radiate in a wavy manner as a gradually broadening band toward the osteoid lamellae of endochondral origin. Calcification is usually not wholly absent, but it takes in only the central parts of the ground substance, the outer layers remaining as osteoid tissue. This explains the abnormal pliability of the diaphyses in rickets and the deformities, especially of the lower extremities, that result from the action of the body-weight.

The most characteristic changes are produced at the epiphyseal lines of the long bones: *i. e.*, in the territory of endochondral ossification.

As it is at this point that the growth in length of the long bones takes place, the phenomena of osteogenesis are studied well here, and all disturbances in the growth of bones find here ready expression.

Even macroscopically or by means of a slight magnification characteristic changes may be seen on the fresh-cut surface of a moderately rickety epiphysis of a rib. First it is seen that the nodular swelling recognized externally as the epiphyseal rings (the so-called "rosary of rickets") corresponds to a great broadening of the cartilage bordering upon the bone. Compared with the surface of a normal rib, it is found that this part corresponds to the zone

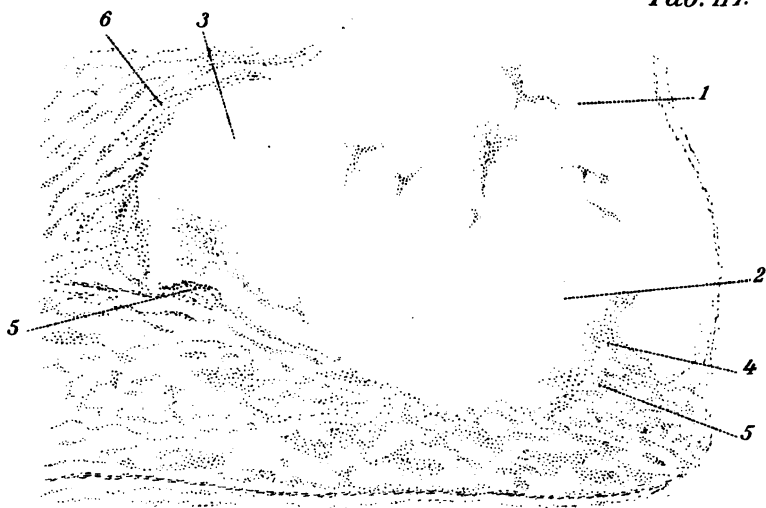


Fig. 1.

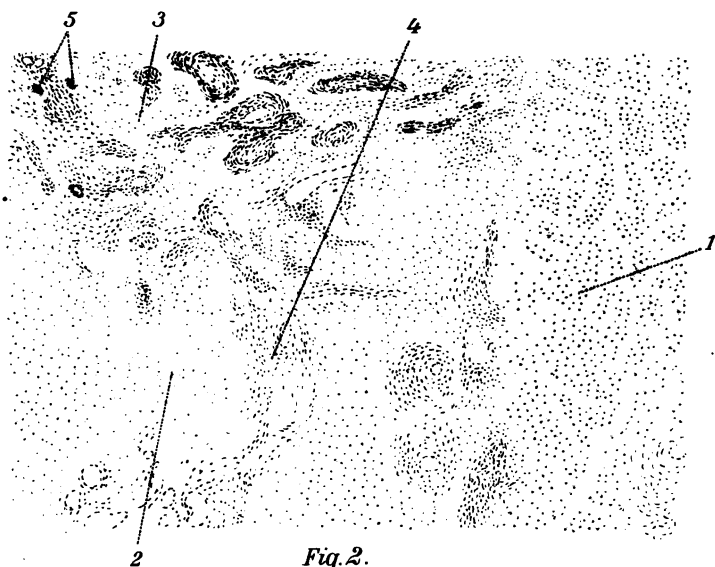


Fig. 2.

of proliferation,—that is, to that area in which the cells of the hyaline cartilage arrange themselves in columns,—while the ground substance disappears and allows confluence of the lacunæ. In the rickety epiphysis the arrangement in the zone of cartilaginous proliferation becomes disturbed, the regular rows of cells are disarranged, and the zone of large-celled cartilage is increased both in length and breadth. Near the quiescent cartilage are found widened lacunæ with two or more cells, but they are arranged in single rhomboid or casket-like groups, with but little ground substance in their interior, while broad bands of ground substance may pass between them (Plate 117, Figs. 1 and 2).

In the normal epiphysis between the border of the zone of cartilaginous proliferation and the bone is a fine, yellowish, transverse line, which the microscope shows to correspond to a preliminary calcification of the ground substance of the large-celled cartilage, a calcification which later disappears as bone lamellæ are deposited by osteoblasts.

In the rickety epiphysis the situation is different; the calcareous deposit is usually very insignificant, and, when present to any extent, it occurs in the form of single, irregularly distributed islands of various extent between the groups of cartilage cells, and it does not present any sharp limitations either on the side toward the bone or on the side toward the hyaline cartilage, but projects irregularly into both zones.

The distinction between the zone of cartilaginous proliferation and the zone of ossification is normally quite linear; the bone trabeculæ end on a straight line along the persisting cartilaginous ground substance, the transition being sharp; and the processes of the medullary tissue extend into the dilated cartilaginous lacunæ to the same extent throughout the whole thickness of the epiphysis. Comparison with the normal of a section through the epiphysis of a rickety rib shows, even on slight magnification,

that the line of junction between the zone of cartilaginous proliferation and of ossification is irregular throughout, and marked by zigzag projections of bone into the cartilage. Between the projections appear deep defects in the cartilage which during life are filled with deep red bone marrow. Microscopic sections show that the marrow sends pointed prolongations into the cartilage as far down as the region of parallel columns of cartilage cells, and sometimes even into the quiescent cartilage (Plate 117, Fig. 1 (4 and 5) and Fig. 2 (4)); that is, through the entire zone of cartilaginous proliferation.

The marrow also shows quantitative and qualitative deviations from the normal. The great increase of red blood cells is especially noticeable, a condition which is referred partly to an inflammatory condition, partly to diminished vitality of the tissue due to the rickety bone changes.

In addition, the bone marrow of rickets contains an unusual number of spindle-shaped cells, while the cells peculiar to marrow, the myelocytes, are greatly reduced in number.

The bone tissue adjacent to the epiphyseal cartilage shows two principal alterations: the spongy trabeculæ formed in the cartilage, as well as by periosteal (perichondral) ossification, show an increased absorption. In the numerous Howship's lacunæ lie many giant cells, "osteoclasts," formed probably by the vascular epithelium and by osteoblasts. In place of the bone thus absorbed there is deposited a substance similar to bone substance in structure, but differing from it chemically by the absence of lime salts—osteoid tissue.

The osteoid substance persists as long as the changes of rickets are acute. Later it is changed into genuine bone by the deposition of lime salts, but by this time extensive curvatures of the shafts and bends of the epiphyses may have formed.

Syphilis.

Congenital syphilis causes typical changes at the epiphyseal lines of the long bones. These changes have a certain similarity to those of rickets, and the two are not infrequently mistaken for each other.

As in rickets, the junction between the cartilage and the spongy bone is not even, but irregularly zigzag, due also to the downgrowth into the cartilage of prolongations from the marrow. The proliferating zone in the cartilage appears broadened, though usually not to the same extent as in the higher grades of rickets; the area of large cartilage cells is increased, but in length rather than in width, the cartilage cells being arranged not in groups, but in rows, and the ground substance frequently appears swollen and softened by mucoid degeneration, so that it runs out jelly-like upon the cut surface (Plate 118, Fig. 2).

The zone of calcareous deposition, on the other hand, is not diminished, as in rickets; on the contrary, it is often increased, though not linearly, as under normal conditions, but in a zigzag line corresponding to the downgrowths of marrow (Plate 118, Fig. 2).

The most striking changes of osteochondritis syphilitica are found in the bone marrow, which appears as a turbid, yellowish, often almost puriform mass, consisting of fattily degenerated round cells, among which are scattered larger and smaller wholly necrotic foci.

The trabeculae of the spongiosa are unusually thin and delicate, widely separated, and subjected to an increased resorption, but there is not the increased deposition of osteoid tissue seen in rickets. On account of the increased absorption and of the changes in the marrow, spontaneous separations may occur between the shaft and the epiphysis, due to the formation between them of an irregular cavity filled with a mass like pus. Transverse fissures may occur in the softened cartilage beyond the zone of calcification.

PLATE 118.

FIG. 1.—**Tuberculous Caries of Costal Cartilage.** $\times 100$. 1, Cartilage; 2, mass of granulation tissue in erosion of cartilage; 3, perichondrium; 4, tubercle with giant cells (5).

FIG. 2.—**Osteochondritis Syphilitica of Costal Epiphysis in Congenital Lues.** $\times 40$. 1, Large-celled cartilage; 2, sprouts from marrow entering cartilage in an irregular manner; 3, preliminary calcification (salts largely removed in preparation of specimen); 4, trabeculae of spongiosa.

In the tertiary form of acquired syphilis specific changes in the bones occur either in the form of chronic, productive, ossifying periostitis, or as gummas which extend into the cortex from the periosteum. Gummatous nodules may form also in the marrow of the long bones. —

Tuberculosis.

Tuberculosis of bones and cartilage presents the same histologic picture. It is most frequently observed as the result of extension from the periosteum and perichondrium into the bone and cartilage. There are also tuberculous processes in the bones of embolic, hematogenous origin, most frequently beginning in the marrow.

In the first form tubercles with giant cells form in the inner layers of the periosteum, the adjacent bone tissue being invaded by a more indifferent granulation tissue, which often contains giant cells that act as osteoclasts (Plate 118, Fig. 1). The osteoclasts must be distinguished from tuberculous giant cells, with which they have nothing to do genetically. The osteoclasts apply themselves to the bone lamellae and cause local resorption of the ground substance; the granulation tissue at once penetrates into the lacunae, which are widened and deepened, while more and more bone is absorbed (rarefying osteitis). Later on, tubercles develop secondarily in the granulation tissue.

It is consequently not the tubercles themselves which

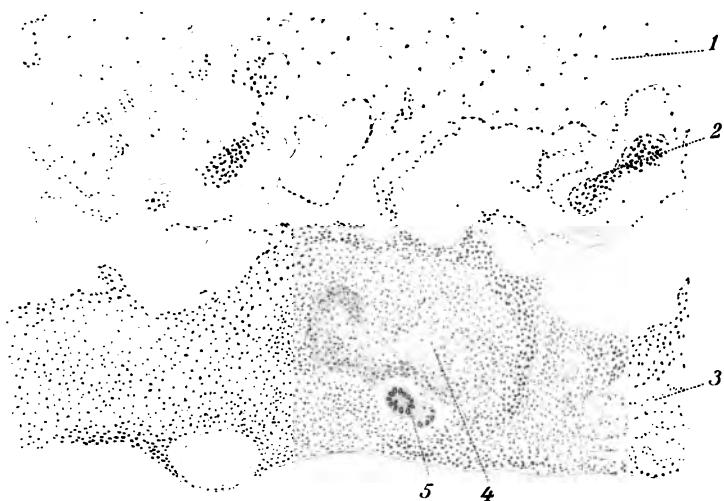


Fig. 1.

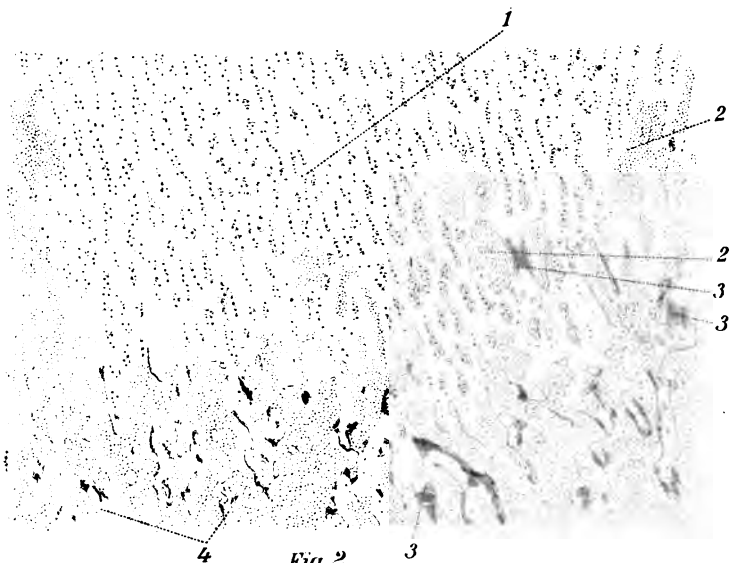


Fig. 2.

lead to absorption (caries) of the bone, but the preceding granulation tissue containing osteoclasts.

Tuberculous chondritis runs a similar course (Plate 118, Fig. 1).

Lacunar absorption of bone lamellæ plays an equally important part in the ordinary purulent osteomyelitis.

Osteomalacia.

Osteomalacia also presents many resemblances to rickets, inasmuch as it is characterized by solution of the calcareous salts and softening of the ground substance of pre-existing bones, combined with the new formation of osteoid non-calcified tissue.

It seems that in osteomalacia there is always an increased apposition of non-calcified lamellæ (Pommer). Sections of compact bone show, as in rickets, interwoven lamellæ of osteoid tissue, which are not seen in normal bones, and which consequently do not arise by decalcification of pre-existing ones, but are newly formed. Furthermore, continuous layers of osteoblasts, which have secreted non-calcified ground substance, point to the new formation of osteoid substance.

In addition, there is a solution of preexisting bone tissue, and this occurs in two ways :

1. By dilatation of medullary spaces and Haversian canals.

2. By enlargement of the so-called bone corpuscles.

Sections of the spongy bone substance, in which the process extends most rapidly and leads to the most extensive, even total, softening (sternum, vertebræ), show the medullary spaces greatly dilated (Plate 119, Fig. 1). The trabeculæ are thin and narrow ; often there are only pointed projections left, the remnants of septa and bridges between the medullary spaces. High powers show the penetration of medullary tissue by narrow, tubular spaces in the trabeculæ, which in many places are partially or wholly penetrated by fine canals, into which grow vessels from the

PLATE 119.

FIG. 1.—**Osteomalacia.** Section of a vertebra. Stained with bleu de Lyon. $\times 80$. The trabeculae of the spongiosa are much thinned, and consist largely of osteoid substance (1), stained blue. Only the central parts are calcified (2), stained red; 3, greatly widened medullary spaces.

FIG. 2.—**Osteomalacia.** From the cortex of ileum; ground preparation. $\times 350$. 3, Osteoid substance in concentric lamellae about the enlarged Haversian canals (2); no bone corpuscles recognizable; 1, enlarged and irregular, partly confluent bone corpuscles, the dilated canals extending into calcified substance without lamellar structure.

marrow. The canals dilate gradually, the vascular sprouts are surrounded with cells, and the perforating canals become large spaces. In this process lacunar absorption, which is typical in tuberculous canals, and also seen in rickets, is generally absent. Lacunae—small depressions in the bone—are not present, as a rule, and for this reason the giant cells or osteoclasts which cause lacunar resorption are also absent.

By suitable staining methods (Plate 119, Fig. 1) may be demonstrated two kinds of substances, even after the lime salts have been dissolved out: An outer layer, the osteoid tissue, which, though free from lime salts, corresponds in its general histologic structure to ordinary bone; and an inner layer, which varies in width according to the stage of the process, and in which the lime salts originally present give a different color with certain stains (red with bleu de Lyon, deep blue with hematoxylin, light red with picrocarmin and methylene-blue). Very high powers show in the osteoid tissue fairly well-preserved bone corpuscles with bone cells, but the fine, tortuous canals, which normally unite the bone corpuscles with one another, are no longer demonstrable. At the border between the calcified and non-calcified tissue there are often lines of fine granules of lime salts.

The compact substance is best examined either in fresh

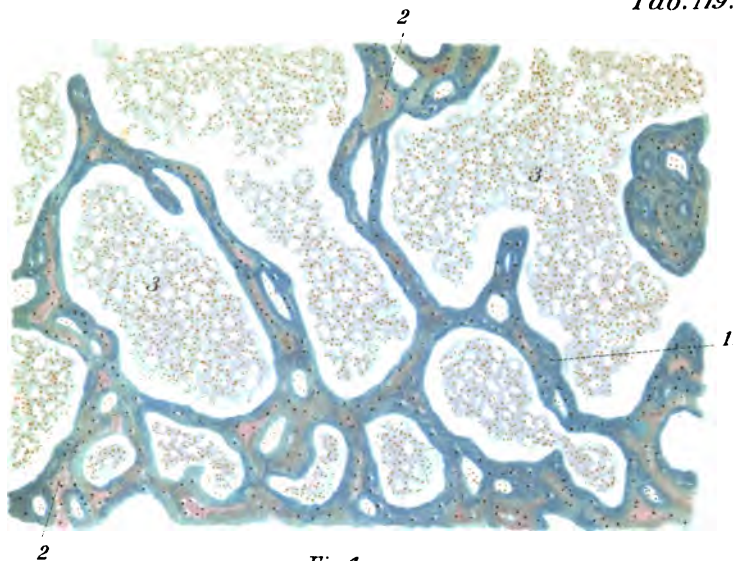


Fig. 1.

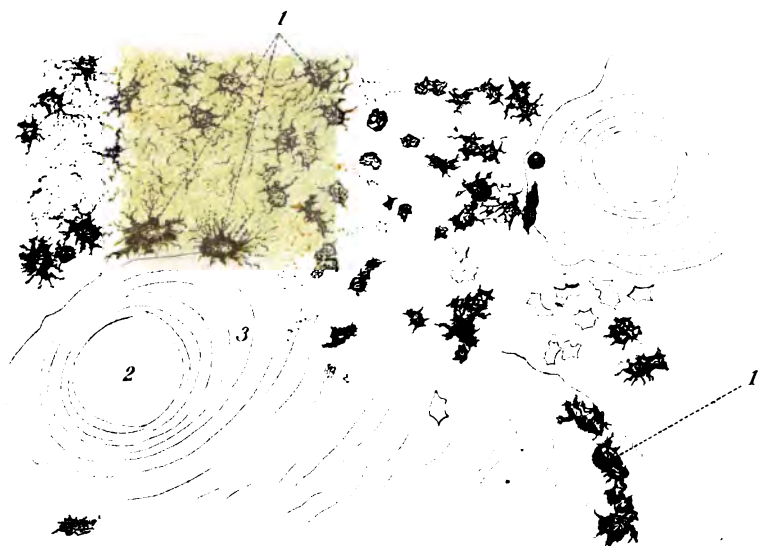


Fig. 2.

sections with the scalpel or by means of ground preparations (Plate 119, Fig. 2).

There is seen a considerable dilatation of the Haversian canals, but they are still cylindrical in form. The adjacent bone substance is deprived of lime salts, but shows a lamellated structure, the bone corpuscles, however, being few or wholly absent. At some distance from the Haversian canals the calcified bone tissue is still present, but the lamellated structure is obscured, and the bone corpuscles show a peculiar condition, which is characteristic for osteomalacia. They are crowded together, extraordinarily large, and irregular in form. Comparison with a normal specimen shows that there is no absolute increase in number, a certain given area does not contain more than normal, but, in consequence of their enlargement, they appear more closely together. They are no longer regularly spindle-formed, but they have assumed atypical and bizarre forms, and confluence is not infrequent (Plate 119, Fig. 2, to the right). The canalicular processes are also widened, thus producing very distinctly the so-called lattice work ("gitterfiguren"). The whole process naturally points to increased resorption of bone substance.

The bone marrow commonly shows changes, but these are in no sense constant and typical. Most frequently the marrow is very rich in blood, and often the other cellular elements are proliferated.

THE JOINTS.

Of the diseases of the joints, two may be noted at this time as interesting from the histologic standpoint: serofibrinous inflammation and the joint changes of gout.

An acute serous articular inflammation associated with fibrinous deposits (synovitis or arthromeningitis serofibrinosa) occurs principally in acute articular rheumatism, in inflammations and purulent processes in the vicinity of the joints, and also as the result of traumatic infection. The joint cavity is filled with a serous exudate, mixed with

PLATE 120.

FIG. 1.—Synovial Membrane of Knee-joint in Acute Serofibrinous Arthromeningitis. $\times 170$. 1, Connective tissue with numerous fibroblasts and accumulations of round cells; 2, blood-vessels filled with leukocytes; 3, blood-vessels filled with fibrinous thrombi.

FIG. 2.—Arthritis Urica. From articular cartilage of lower femoral epiphysis. $\times 127$. 1, Cartilage; 2, dense deposits of urates; 3, crystals of sodic urate extending into cartilage.

fibrinous flocculi, and the capsule and synovial membrane are edematous and swollen. The inner surface of the latter may be covered with a delicate fibrinous layer, the threads of which partly lie on the surface, partly extend between the epithelium into the underlying tissue, the epithelium after a time being destroyed, just as in fibrinous inflammation of a serous membrane like the pleura (Vol. I, p. 117). The synovial membrane also shows, in addition to swelling of the connective-tissue fibers, marked multiplication of the fixed cells and a diffuse round-cell infiltration, now with lymphocytes, now with leukocytes. Spindle-shaped epithelioid cells (fibroblasts) form the principal part of the inner layers.

The vessels of the synovial membrane, arterial as well as venous, are greatly dilated and nearly all filled with thrombi of interlacing fibrinous threads mixed with white blood cells; others are densely crowded with white cells (Plate 120, Fig. 1).

When pyogenic agents, as staphylococci, streptococci, pneumococci, and gonococci, reach the joint membranes, as may occur in pyemia and endocarditis by way of embolism, then suppuration rapidly develops around the infectious emboli which oftenest are arrested in the villous prolongations. The suppuration may extend to the cartilage and to the bone. Suppurative inflammations may extend to the synovial membranes from the bones and the marrow.

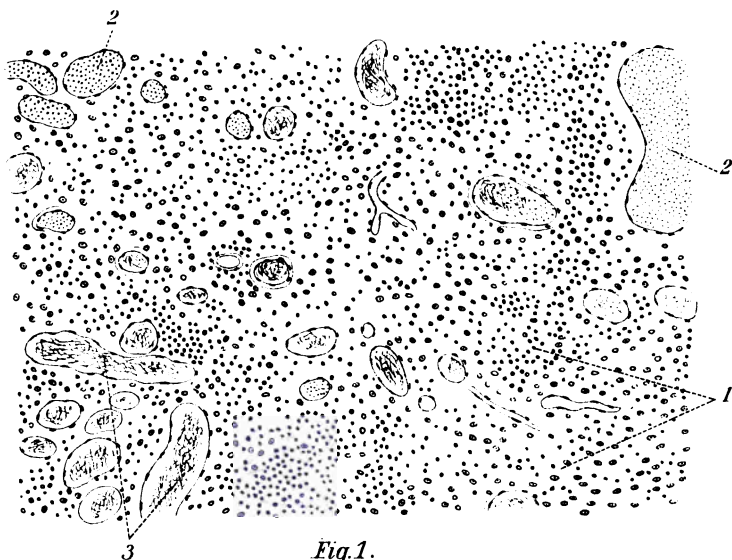


Fig. 1.

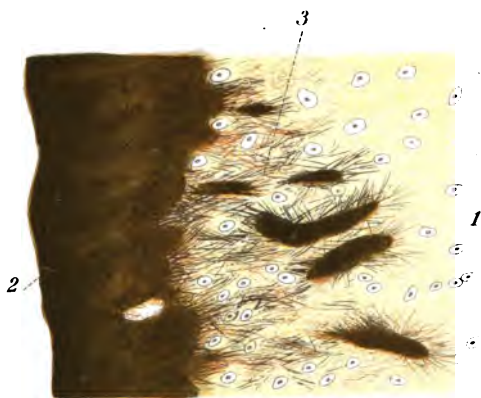


Fig. 2.

Tuberculosis of the joints is very often associated with a sero-fibrinous synovitis, especially in the initial stages, but, in addition, there develop typical tubercles. If the process extends to the articular cartilages, the substance of the latter may undergo metaplasia into mucoid tissue.

Arthritis Urica.

In gout there occurs a deposition of urates (calcium and sodium), especially into the articular cartilages. Even macroscopically the cartilages may present a white covering, as if smeared with oil.

Fresh sections by means of a razor show most clearly dense bundles of uratic crystals extending into the cartilages as fine needles. At the outer margin the crystals are amalgamated into opaque, in transmitted light almost black masses, from which they radiate into the cartilage. The lacunæ are penetrated, the cells die, and the spaces dilate (Plate 120, Fig. 2).

The deposition of urates in the articular fibrous tissue leads to the development of granulation tissue, which usually contains a large number of giant cells in consequence of the action of the foreign bodies upon the connective tissue.

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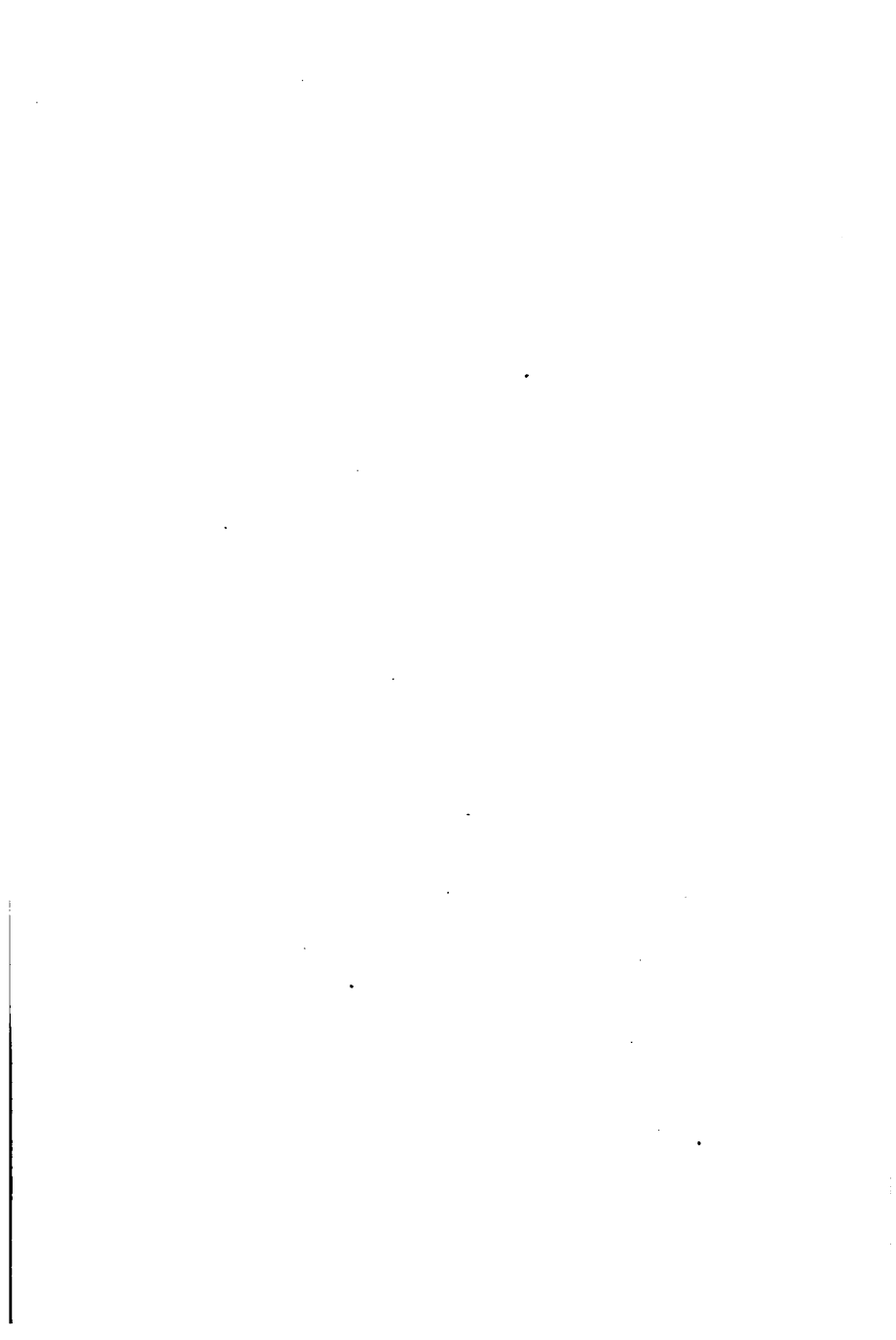
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